The Diagnostic and Therapeutic Management of Pulmonary Embolism

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CHAPTER 1

General introduction and outline

Pulmonary embolism (PE) is defined as an obstruction of a pulmonary artery caused by a thrombotic embolus and was first described by Virchow in 1846 [1]. PE shares many characteristics of epidemiology and pathophysiology with deep vein thrombosis (DVT) and they are generally considered as two different presentations of the same disease called venous thromboembolism (VTE). With an annual rate of 1-2 per 1000 patients, PE is a relatively common disease [2-3]. A rapid diagnosis and accurate treatment is essential, since PE can be a fatal disease.

The diagnostic management of suspected acute PE is challenging due to the non-specific and highly variable signs and symptoms. As a consequence, the diagnosis has to be confirmed by a reliable objective test, which is nowadays computed tomography pulmonary angiography (CTPA) [4]. Many efforts have been made to exclude PE without the use of CTPA, since unrestricted use of CTPA is associated with several disadvantages, being radiation exposure, complications related to the administration of intravenous contrast and high health-care costs. An overview of the current diagnostic management strategies, as well as current therapeutic management strategies, is presented in **chapter 2**.

The first part of this thesis focuses on the diagnostic management of suspected acute PE. First, we thoroughly investigated the performance of the currently most commonly applied diagnostic management strategy. In **chapter 3**, a systematic review and patient-level meta-analysis is described that investigated the performance of the Wells clinical decision rule combined with a quantitative D-dimer test in order to exclude acute PE without CTPA, which is the most commonly used diagnostic strategy. The aim of **chapter 4** was to determine whether a normal CTPA alone is a safe criterion to rule out acute PE, particularly in patients with the highest clinical probability. Second, we evaluated two alternative diagnostic strategies in an attempt to further improve the efficiency, i.e. reducing the number of required CTPA, while maintaining the high safety of the diagnostic management. **Chapter 5** discusses the potential of applying an increased D-dimer threshold in patients with the lowest clinical probability. The results from the YEARS study, a prospective multicentre cohort study investigating a simplified and more efficient diagnostic management strategy are provided in **chapter 6**.

The topic of the second part of this thesis is the therapeutic management of acute VTE. One of the key developments of recent years is the introduction of the direct oral anticoagulants for the treatment of acute VTE. In **chapter 7**, a meta-analysis is provided on the effectiveness and the safety of these drugs compared to vitamin K antagonists. The safety of considering a limited duration of anticoagulant treatment in patients with a second VTE that occurred after a relatively long interval, as recommended in the Dutch guideline and only based on indirect evidence, was evaluated in **chapter 8**. In the following chapters, some issues on the management of cancer-associated VTE are addressed. In **chapter 9**, the current recommendations regarding treatment duration

for cancer-associated VTE are evaluated, particularly whether it is safe to stop anticoagulant treatment in patients cured from cancer. In **chapter 10**, the evidence from phase 3 studies on the efficacy and safety of the direct oral anticoagulants in patients with a cancer-associated VTE is summarized in a meta-analysis. The final chapter focusses on PE diagnosed on computed tomography scanning not performed for suspected PE, the so called incidental PE. Incidental PE is a growing challenge for clinicians, particularly in cancer patients. Although it is a relatively common diagnosis the evidence regarding the optimal management is scarce. In **chapter 11**, we combined results from 11 individual cohort studies in order to provide the best available evidence on the management of incidental PE in cancer patients.

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CHAPTER 2

Recent developments in the diagnosis and treatment of pulmonary embolism

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ABSTRACT

Due to the nonspecific symptoms of the condition, a diagnosis of acute pulmonary embolism (PE) is frequently considered. However, PE will only be confirmed in 10–20% of patients. Because the imaging test of choice, computed tomography pulmonary angiography (CTPA), is costly and associated with radiation exposure and other complications, a validated diagnostic algorithm consisting of a clinical decision rule and D-dimer test should be used to safely exclude PE in 20–30% of patients without the need for CTPA. Recently, the age-adjusted D-dimer threshold has been validated, and this has increased the proportion of patients at older age in which PE can be excluded without CTPA. Initial therapeutic management of PE depends on the risk of short-term PE-related mortality. Haemodynamically unstable patients should be closely monitored and receive thrombolytic therapy unless contraindicated because of an unacceptably high bleeding risk, whereas patients with low-risk PE may be safely discharged early from hospital or receive only outpatient treatment. The PESI score and Hestia decision rule are available to select patients in whom early discharge or outpatient treatment will be safe, although the safety of these strategies should be confirmed in additional studies. Standard PE therapy consists of low molecular weight heparin (LMWH) followed by vitamin K antagonists (VKAs). Recently, several nonvitamin K-dependent oral anticoagulants have been shown to be as effective as LMWH/VKAs, and maybe safer. Determining the optimal duration of treatment for a first unprovoked PE remains a challenge, although clinical prediction rules for estimating the risk of recurrence of venous thromboembolism and anticoagulation-associated haemorrhage are under investigation. Using these prediction rules may lead to both more standardized and more individualized long-term treatment of PE.

INTRODUCTION

Acute pulmonary embolism (PE) is a relatively common disease with an annual rate of 1–2 per 1000 patients [1, 2]. The clinical presentation of acute PE is nonspecific and highly variable, ranging from incidentally diagnosed asymptomatic thrombi to sudden death [3]. As a result, a clinical suspicion of PE is frequently raised, whilst the diagnosis is only confirmed in 10–20% of patients [4, 5]. Diagnostic algorithms have been developed to ensure reliable and efficient management of patients with clinically suspected PE.

Once acute PE is diagnosed, prompt initiation of anticoagulant therapy is indicated to prevent thrombus extension and recurrent (fatal) PE. However, the risk of such an adverse outcome is highly variable, ranging from <1% to >15% [6]. Management decisions including early discharge or prescription of thrombolytic therapy should preferably be based on reproducible risk stratification of the individual patient [6, 7]. For the long-term treatment of acute PE, the decision to continue or stop anticoagulant therapy, after an initial period of 3 months, depends on the balance between the risk of recurrent venous thromboembolism (VTE) and of anticoagulant-associated haemorrhage.

Here, we will present an up-to-date overview of the therapeutic management of established PE, discussing conventional medical therapy, the recently introduced non-vitamin K-dependent oral anticoagulants (NOACs), outpatient treatment, thrombolytic therapy and the duration of treatment. In particular, we will focus on recent advances as a follow-up to a review of a similar topic published in this journal in 2010 [8].

DIAGNOSTIC MANAGEMENT OF CLINICALLY SUSPECTED ACUTE PE

Symptoms that may suggest the presence of acute PE are the sudden onset of dyspnoea, pleuritic chest pain, haemoptysis, extremity swelling suggestive of deep vein thrombosis (DVT) and syncope [3]. Of note, these symptoms are nonspecific for PE and may also be present in many other acute cardiopulmonary conditions. In large diagnostic management studies, the PE prevalence amongst patients with a clinical suspicion of PE ranged from 10% to 30% [4, 5, 9]. PE can only be diagnosed using an imaging test, at present usually computed tomography pulmonary angiography (CTPA), which is associated with high healthcare costs, radiation exposure and a risk of complications such as contrast-induced nephropathy and allergic reactions [10-12]. Therefore, diagnostic management algorithms have been developed to exclude PE without the need for imaging tests in a proportion of patients. These algorithms start with a clinical decision rule (CDR), which predicts the clinical pretest probability of PE, followed by a D-dimer blood test and/or a CTPA.

CDRs and D-dimer testing

Various CDRs have been standardized and validated for use in clinical practice, of these, the Wells rule and revised Geneva score are the most widely validated for PE **(Table 1)** [13, 14]. Originally, different items were awarded different scores, but for practical reasons, both rules have been simplified by assigning only one point to each item, without lowering their diagnostic accuracy [15, 16]. The CDRs are used to categorize patients into either 'PE unlikely' or 'PE likely' groups, with PE prevalences of 12–17% and 37–43%, respectively, in European cohorts [4, 5]. The accuracy of the original and simplified versions of the Wells rule and revised Geneva score were shown to be similar, and the choice of a specific rule may therefore depend on local preference [4].

Table 1. Clinical decision rules.

Item	Original version	Simplified version
Wells rule		
Previous PE or DVT	1.5	1
Heart rate >100 beats/min	1.5	1
Surgery or immobilization within 4 weeks	1.5	1
Haemoptysis	1	1
Active malignancy	1	1
Clinical signs of DVT	3	1
Alternative diagnosis less likely than PE	3	1
Clinical probability categories		
PE unlikely	≤4	≤1
PE likely	>4	>1
Revised Geneva score		
Previous DVT or PE	3	1
Heart rate 75–94 beats/min	3	1
Heart rate ≥95 beats/min	5	2
Surgery or fracture within 1 month	2	1
Haemoptysis	2	1
Active malignancy	2	1
Unilateral lower limb pain	3	1
Pain on lower limb deep vein palpation and unilateral oedema	4	1
Age >65 years	1	1
Clinical probability categories		
PE unlikely	≤ 5	≤2
PE likely	> 5	>2

Note: DVT, deep vein thrombosis; PE, pulmonary embolism.

The D-dimer level in plasma is a marker of fibrinolysis and is elevated in the presence of acute VTE as well as in many other clinical conditions. The sensitivity of D-dimer testing for the latest generation of assays is very high (95–100%), whereas the specificity is moderate (43–93%) [17]. Accordingly, using the standard threshold of <500 µg/L, the negative predictive value of D-dimer testing allows for the exclusion of PE in patients with a PE unlikely clinical probability [4, 5, 9]. By applying this strategy, PE can be ruled out in 25–46% of patients without performing an imaging test, with a 3-month VTE incidence of 0.04–0.96% after anticoagulant therapy is withheld [18].

Recently, attempts have been made to increase the number of patients in whom PE can be ruled out without imaging tests. As D-dimer levels increase with age, an age-dependent D-dimer cut-off level was proposed: age × 10 µg/L in patients over 50 years of age [19]. The safety of applying this age-dependent D-dimer cut-off was recently confirmed in a large prospective outcome trial [9]. The 3-month VTE incidence in patients in the PE unlikely category and with a D-dimer level >500 µg/L but below the age-adjusted threshold was only 0.3% (95% confidence interval (CI) 0.1–1.7). The absolute increase in the proportion of patients above 50 years old that could be managed without CTPA was 11.6%. In particular, patients aged 75 years and older could be more frequently managed safely without CTPA.

Imaging tests

The historical gold standard imaging test for diagnosing PE is pulmonary angiography, which is associated with a 3-month VTE incidence after a negative result of 1.7% (95% CI 1.0–2.7) [20]. Because pulmonary angiography is an invasive procedure, this test was first replaced by ventilation-perfusion lung scanning (V/Q scanning) and later by CTPA. Although it has been demonstrated that V/Q scanning is safe for excluding PE, with a 3-month VTE incidence of only 0.9% (upper limit of 95% CI 2.3) after a normal result, its major disadvantage is an inconclusive result in 28–46% of patients, in whom the PE prevalence is still 10–30% and who thus require an additional imaging test [21, 22]. CTPA results in an inconclusive test result in only 0.9–4.6% of patients [23]. Furthermore, CTPA is more widely available with faster acquisition and the possibility of establishing an alternative diagnosis, although the value of the latter has recently been questioned [24]. A possible advantage of V/Q scanning is the lower radiation exposure compared to CTPA (1.1 vs. 2–6 mSv), which may be relevant for specific patient groups, particularly young (particularly female) patients and pregnant women. V/Q scanning may also be considered for patients with a known allergy to contrast medium [11, 12].

The sensitivity of multidetector row high-resolution CTPA is excellent and several outcome studies have consistently demonstrated the safety of withholding anticoagulant therapy in patients with a negative CTPA alone [23]. In a meta-analysis, the pooled 3-month VTE incidence after a negative CTPA alone in patients in whom CTPA was

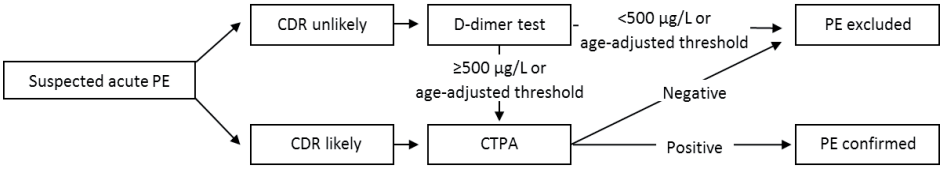
indicated based on a validated CDR and/or D-dimer test was 1.2% (95% CI 0.8–1.8), compared to 1.1% (95% CI 0.6–2.0) after negative CTPA and subsequently negative lower limb compression ultrasonography, indicating that the safety could not be further improved by excluding asymptomatic DVT after a negative CTPA [23]. In addition to ionizing radiation, other potential concerns related to the easily available CTPA as the first-line imaging test are an increased incidence of contrast-induced nephropathy, a risk of unsuspected findings requiring additional medical attention and an increased incidence of isolated subsegmental PE, of which the clinical relevance has become increasingly under debate [10, 25-27].

Integrated approach

The first step in the diagnostic management of patients with clinically suspected acute PE is to determine whether the patient has signs and symptoms of haemodynamic shock. If so, patients should be immediately referred for additional imaging tests and thrombolytic therapy should be started without waiting for a CDR result or D-dimer level.

In patients who are haemodynamically stable, diagnostic management starts with the assessment of the clinical probability of PE using one of the validated CDRs (**Table 1**). In patients with a PE unlikely clinical probability, a D-dimer test is indicated and PE can be ruled out without further imaging tests if the level is <500 µg/L or below the age-adjusted threshold for patients over the age of 50 years. In the remaining patients with either a PE unlikely CDR score in combination with an elevated D-dimer level or a PE likely CDR score, CTPA is indicated to determine the presence of PE (**Figure 1**).

Figure 1. Integrated approach for clinically suspected acute pulmonary embolism in haemodynamically stable patients.



Note: CDR, clinical decision rule; CTPA, computed tomography pulmonary angiography; PE, pulmonary embolism.

Correct use of a validated diagnostic algorithm is required to ensure its safety; this is highlighted by several recent studies showing that a validated diagnostic algorithm is frequently not or incorrectly applied. This leads to the unnecessary use of CTPA and, even more relevant, to a higher 3-month VTE incidence in patients in whom anticoagulant therapy is withheld [28]. A promising intervention to improve adherence may be the implementation of computerized clinical decision support for clinicians [29]. Future studies should focus on further simplification of the diagnostic algorithms to improve

the compliance and consequently the safety and efficiency of diagnostic management in daily clinical practice. Future studies should also investigate whether increasing the D-dimer threshold, for instance with variable D-dimer thresholds depending on the pretest probability, may further improve the efficiency without reducing the safety of the diagnostic algorithm [30].

TREATMENT OF ACUTE PE

Risk stratification of acute PE

Patients with acute PE should be stratified according to the short-term PE-related mortality risk. Risk stratification starts with identifying patients in haemodynamic shock, who are classified as having high-risk or massive PE with an estimated 30-day PE-related mortality risk of >15% [7].

For the remaining haemodynamically stable patients, the ability of clinical prediction rules and several tests to distinguish patients with a low risk (<1%) from those with an intermediate risk (3–15%) of an adverse outcome has been investigated [7].

The Hestia decision rule consists of a set of criteria that can be used to select patients with low-risk PE who are candidates for early discharge or outpatient treatment (**Table 2**) [31]. The major strength of the Hestia decision rule is its clinician friendliness, as it consists of only 11 easy-to-use bedside criteria that should all be negative before early discharge or outpatient treatment can be considered. The Pulmonary Embolism Severity Index (PESI), which combines several clinical signs, symptoms and comorbidities (**Table 3**), is also available and is able to identify patients at low risk of short-term PE-related mortality [6]. To overcome its complexity, a simplified version (sPESI) has been proposed [32].

In addition to the Hestia decision rule and the PESI, several laboratory biomarkers have been shown to predict adverse outcome in haemodynamically stable patients. High concentrations of brain-type natriuretic peptides (BNPs) or the N-terminal of the prohormone of BNP (NT-proBNP) that are elevated during PE-associated right ventricular (RV) overload are strongly associated with mortality in acute PE with an OR of 7.6 (95% CI 3.4–17), whereas normal levels identify patients with a low risk of short-term PE-related mortality (17% vs. 1.7%) [33]. In addition, elevated plasma troponin I or (high-sensitivity) troponin T levels are associated with a high risk of short-term mortality (18% vs. 2.3%) in haemodynamically stable patients with an OR of 5.90 (95% CI 2.7–13) [34].

Both echocardiography and CTPA images can be used to detect RV dysfunction, which is also associated with an elevated risk of short-term PE-related mortality in patients who are haemodynamically stable. At least 25% of patients with PE have signs of RV dysfunction on echocardiography, such as RV dilatation, an increased RV/left ventricular (LV) diameter ratio, hypokinesia of the free RV wall, increased tricuspid regurgitation

Table 2. Hestia decision rule.

Haemodynamically unstable?[a]
Thrombolysis or embolectomy necessary?
High risk of bleeding?[b]
Oxygen supply to maintain oxygen saturation >90% for more than 24 h?
Pulmonary embolism diagnosed during anticoagulant treatment?
Intravenous pain medication for more 24 h?
Medical or social reason for treatment in hospital for more than 24 h?
Creatinine clearance <30 mL/min?[c]
Severe liver impairment?[d]
Pregnant?
Documented history of heparin-induced thrombocytopenia?
Interpretation
If the answer to at least one of the above questions is 'YES', the patient cannot be treated as an outpatient

Note: [a]Includes, at the discretion of the physician, systolic blood pressure <100 mmHg with heart rate >100 beats/min; condition requiring admission to an intensive care unit; [b]gastrointestinal bleeding in the preceding 14 days, recent stroke (within 4 weeks), recent operation (within 2 weeks), bleeding disorder or thrombocytopenia (platelet count <75 x 10^9/L) and/or uncontrolled hypertension (systolic blood pressure >180 mmHg or diastolic blood pressure > 110 mmHg); [c]creatinine clearance calculated according to the Cockroft–Gault formula; [d]at the discretion of the treating physician.

jet velocity or decreased tricuspid annulus plane systolic excursion. Echocardiographic signs of RV dysfunction in haemodynamically stable patients with PE are associated with an OR of 2.4 (95% CI 1.3–4.3) for short-term mortality [35]. The RV/LV dimensional ratio can also be assessed on axial or reconstructed four-chamber CTPA views, for which thresholds of ≥0.9 or ≥1.0 are generally used. CTPA-assessed RV dysfunction in haemodynamically stable patients is associated with an increased risk of short-term mortality (7.8% vs. 5.1%) as well as with short-term PE-related mortality (2.2% vs. 0.2%) with ORs of 1.8 (95% CI 1.3–2.6) and 7.4 (95% CI 1.4–40), respectively [36]. Interestingly, several studies have shown that models combining prediction rules, biomarkers and imaging tests improve the predictive accuracy compared with the individual tests, although at present, none of these combinations can be recommended to guide management in daily clinical practice [37, 38].

Management of high-risk patients

Thrombolytic therapy is able to rapidly resolve thromboembolic obstruction enabling prompt reduction in pulmonary artery pressure and improvement in RV function. The results of one study suggested that a clinical and echocardiographic improvement can be observed in more than 90% of patients who receive thrombolysis [39]. Thrombolytic therapy is generally recommended for high-risk patients with PE with overt haemodynamic instability without a high risk of bleeding complications, although there is a lack

Table 3. PESI score.

Parameter	Original version	Simplified version
Age	Age in years	*1 point (if age >80 years)*
Male sex	+10 points	
Cancer	+30 points	1 point
Chronic heart failure	+10 points	1 point
Chronic pulmonary disease	+10 points	
Heart rate ≥110 beats/min	+20 points	1 point
Systolic blood pressure <100 mmHg	+30 points	1 point
Respiratory rate >30 breaths/min	+20 points	
Temperature <36 °C	+20 points	
Altered mental status[a]	+60 points	
Arterial oxygen saturation <90%[b]	+20 points	1 point
Risk strata		
	Class I: ≤65 points very low 30-day mortality risk 0–1.6%	0 points = 30-day mortality risk 1.0% (95% CI 0–2.1)
	Class II: 66–85 points low mortality risk 1.7–3.5%	≥1 point(s) = 30-day mortality risk 10.9% (95% CI 8.5–13.2)
	Class III: 86–105 points moderate mortality risk 3.2–7.1%	
	Class IV: 106–125 points high mortality risk 4.0–11.4%	
	Class V: >125 points very high mortality risk 10.0–24.5%	

Note: PESI, Pulmonary Embolism Severity Index. [a]Defined as disorientation, lethargy, stupor or coma. [b]With and without the administration of supplemental oxygen.

of convincing supporting evidence from large randomized controlled trials. A meta-analysis of randomized trials including haemodynamically unstable patients with PE demonstrated an OR of 0.53 (2.2% vs. 3.9%; 95% CI 0.32–0.88) for recurrent PE and death in patients who received thrombolytic therapy [40]. In addition, in an epidemiological study, haemodynamically unstable patients with PE who received thrombolytic therapy had a relative risk of 0.2 (95% CI 0.19–0.22) for PE-related in-hospital death compared to those who had not received thrombolytic therapy [41]. Of major concern, it was shown in a recent meta-analysis that thrombolytic therapy substantially increased the risk of major bleeding complications with an OR of 2.73 (9.2% vs. 3.4%; 95% CI 1.91–3.91) compared to standard anticoagulant treatment [40]. Percutaneous catheter-directed therapy and surgical embolectomy are alternatives to thrombolytic therapy, for example

in the case of a contraindication to thrombolysis or after thrombolytic therapy has failed or is deemed inadequate as first-line treatment, although these interventions have not been investigated in clinical outcome studies [42].

Management of nonhigh-risk patients

Amongst the nonhigh-risk haemodynamically stable patients, two key questions with regard to therapeutic management remain to be answered: (i) Do patients with intermediate-risk PE benefit from thrombolytic therapy? (ii) Which patients with low risk of adverse outcome are suitable candidates for outpatient treatment or early discharge?

The benefit of administering thrombolytic drugs to haemodynamically stable patients with intermediate-risk PE has been debated for many years. Individual small randomized trials have consistently demonstrated that thrombolytic therapy reduces the risk of haemodynamic deterioration and recurrent PE, at the cost of a higher risk of major haemorrhage without an effect on overall mortality [40, 43]. In 2014, the results of the randomized double-blind PEITHO trial were published. This study investigated the effects of a single dose of tenecteplase (varying from 30 to 50 mg depending on body weight) versus placebo in 1006 patients with an intermediate risk of PE [44]. Intermediate-risk PE was defined as a PESI score of III–V, elevated biomarkers of cardiac injury and signs of RV dysfunction on echocardiography or CTPA. The study demonstrated a significant reduction in the primary efficacy outcome (a composite of all-cause death or haemodynamic deterioration within 7 days of randomization), with an OR of 0.44 (2.6% vs. 5.6%; 95% CI 0.23–0.88). However, 7-day mortality was not different between the two groups: 1.2% of patients who received tenecteplase and 1.8% of patients who received placebo (OR 0.65; 95% CI 0.23–1.85). Of interest, patients who were randomly assigned to receive tenecteplase had a significantly higher risk of major extracranial bleeding and (predominantly haemorrhagic) stroke within 7 days with ORs of 5.6 (6.3% vs. 1.2%; 95% CI 2.3–13.4) and 12 (2.4% vs. 0.2%; 95% CI 1.6–93.4), respectively. It should be noted that only 23 patients (4.6%) from the placebo cohort eventually received rescue thrombolysis during follow-up because of in-hospital haemodynamic deterioration, and two of these patients died within 7 days.

In conclusion, thrombolytic therapy in haemodynamically stable intermediate-risk patients with PE reduces the risk of the composite endpoint consisting of haemodynamic deterioration and death at the cost of an increase in the incidence of major haemorrhage. Therefore, thrombolytic therapy cannot be recommended for haemodynamically stable intermediate-risk patients with PE. These patients should receive standard anticoagulant therapy and close monitoring, whilst thrombolytic therapy should be reserved for patients with haemodynamic deterioration during the first days of treatment.

One randomized trial and two cohort studies evaluating outpatient treatment or early discharge for patients with PE have been completed and the results published. In the

largest study reported to date, there were initially 14 exclusion criteria (**Table 4**) and thereafter patients with a PESI class I or II were selected [45]. Patients were randomly assigned to either conventional in-hospital treatment or outpatient treatment (discharge after a mean of 0.5 days). Of the 1557 patients screened, 470 (30%) were potentially eligible for early discharge (<24 h) of whom 344 were eventually enrolled in the study. Only one of the 171 (0.6%) evaluable patients receiving outpatient treatment developed a nonfatal recurrent VTE during the 3-month follow-up, and two patients (1.2%) had a major haemorrhage within 14 days. Amongst the 168 evaluable patients treated in hospital, neither recurrent VTE nor major haemorrhage occurred within 14 days. Based on these results, the authors concluded that outpatient treatment was noninferior to in-hospital treatment [45]. A major limitation of this strategy is the complexity of scoring the 11 (items) of the PESI score combined with the many other exclusion criteria that were used in the study. Although this limitation may be partly overcome using the sPESI, it should be noted that the simplified score has not been validated in a prospective management study.

Table 4. Exclusion criteria in a randomized trial investigating outpatient treatment amongst PE patients with a PESI class I or II (from Aujesky et al. [45]).

Arterial hypoxaemia (oxygen saturation on room air <90% measured by pulse oximetry or a partial pressure of oxygen <60 mmHg on arterial blood gas analysis)
Systolic blood pressure <100 mmHg
Chest pain necessitating parenteral administration of opioids
Active bleeding or high risk of bleeding (defined as stroke during the preceding 10 days)
Gastrointestinal bleeding during the preceding 14 days or platelet count <75 x 10^9/L
Severe renal failure (creatinine clearance <30 mL/min based on the Cockcroft–Gault equation)
Extreme obesity (body mass >150 kg), history of heparin-induced thrombocytopenia or allergy to heparins
Therapeutic oral anticoagulation at the time of diagnosis of PE (INR ≥2·0)
Any barriers to treatment adherence or follow-up (e.g. current alcohol abuse, illicit drug use, psychosis, dementia or homelessness)
Pregnancy
Imprisonment
Diagnosis of pulmonary embolism >23 h before the time of screening (to avoid enrolling already stabilized patients)
Previous enrolment in the trial

Note: INR, international normalized ratio; PE, pulmonary embolism; PESI, Pulmonary Embolism Severity Index.

The Hestia decision rule has also been evaluated a. a selection tool for outpatient treatment (**Table 2**) [31]. In a prospective cohort study, 297 (51%) of the 581 consecutive patients with acute PE were selected for outpatient treatment of whom six (2.0%) experienced a nonfatal recurrent VTE. Two patients (0.7%) experienced a major haemor-

rhage, one (0.3%) of whom suffered fatal intracranial bleeding. The major advantages of this strategy are the clinician friendliness and the high degree of simplicity.

NT-proBNP has also been evaluated in a cohort study as a tool for selecting patients for outpatient treatment [46]. Haemodynamically stable patients with a low NT-proBNP concentration (threshold <500 pg/mL) were discharged within 24 h of diagnosis. Of the 351 patients in this cohort, 152 (43%) were treated as outpatients and none developed a recurrent VTE or major haemorrhage or died during 3 months of follow-up [46]. In the Vesta study, the results of which will be presented at the congress of the International Society of Thrombosis and Haemostasis in June 2015, a total of 550 patients were randomly assigned to the Hestia decision rule combined with an NT-proBNP test or the Hestia decision rule alone (NTR2603). Of the 275 patients managed according to the Hestia decision rule in combination with an NT-proBNP test, 34 (12%) had a concentration of NT-proBNP >500 ng/L and were managed as inpatients. None of these patients suffered from the primary outcome (30-day adverse outcome defined as PE or bleeding-related mortality, cardiopulmonary resuscitation or admission to the intensive care unit). Of the 275 patients managed according to the Hestia decision rule alone, three (1.1%; 95% CI 0.2–3.2) experienced the primary outcome, all of whom had a normal NT-proBNP level, which were determined in a post hoc analysis. Therefore, the findings of this study confirm the safety of selecting patients who can be treated as outpatients and suggest that NT-proBNP measurements are of limited additional value.

In conclusion, it has been shown that outpatient treatment of patients with PE based on the Hestia decision rule or a combination of several exclusion criteria and the PESI score is safe. Of note, neither the PESI nor the sPESI rule has been evaluated as a sole test to select patients for outpatient treatment. The combination of a clinical prediction rule, laboratory biomarkers and/or findings on imaging tests to further optimize the identification of patients who can be safely managed in the outpatient setting remains to be evaluated.

Initial anticoagulant therapy (first 3 months)

Acute PE requires initial treatment with a direct-onset anticoagulant drug to prevent the extension of thrombosis or fatal recurrent VTE [7, 47]. Weight-adjusted subcutaneous low molecular weight heparin (LMWH) is the treatment of choice for the large majority of patients. Intravenous unfractionated heparin is reserved for patients with severe renal impairment (creatinine clearance <20–30 mL/min), patients with a high risk of haemorrhage including those receiving thrombolytic therapy, haemodynamically unstable patients and individuals who are extremely overweight or underweight. Fondaparinux is an alternative to LMWH and unfractionated heparin in patients with (a history of) heparin-induced thrombocytopenia [7, 48]. Monitoring of the anticoagulant effect of LMWH by determining the antifactor Xa activity is not generally recommended, although it can

be considered in specific circumstances (i.e. in patients with moderate renal impairment or during pregnancy). The target range measured 4 hours after administration is 1.0–2.0 IU/mL for once-daily administration and 0.6–1.0 IU/mL for twice-daily administration of LMWH [7].

Patients with acute PE should be treated for at least 3 months. For decades, vitamin K antagonists (VKAs) have been the long-term treatment of choice and must be started in parallel with one of the parenterally administered direct-onset anticoagulant drugs for at least 5 days and until the international normalized ratio (INR) has reached a therapeutic range (between 2.0 and 3.0) on 2 consecutive days. VKA therapy is highly effective with a rate of recurrent VTE of 3–4% during the initial 3 months of therapy [49]. It has been estimated that the rate of major haemorrhage during the initial 3 months of VKA therapy is 1–2% [49]. A major disadvantage of VKA therapy is the need for frequent laboratory monitoring of the INR with tailored dosing, as a result of the variable pharmacokinetic and pharmacodynamic parameters, and interactions with food and drugs [50].

In recent years, several NOACs have become available for anticoagulant therapy (**Table 5**). These drugs directly and specifically inhibit either thrombin (factor II) or factor Xa. The major advantage of this new drug class is the simplification of PE treatment, due to the rapid onset of action, the predictable anticoagulant effect and a low potential for drug and food interactions [50]. Rivaroxaban and apixaban were investigated with an initial higher dose for 3 weeks and 7 days, respectively, without the need for preceding LMWH therapy, whereas dabigatran and edoxaban were administered after a mean period of 10 days of treatment with LMWH. These drugs can be prescribed in fixed doses and routine laboratory monitoring is not required. A noninferior efficacy compared to standard treatment with VKA has been demonstrated for all NOACs individually in phase III trials [51-55] and confirmed in a meta-analysis: the risk ratio for recurrent VTE was 0.9 (95% CI 0.7–1.1) [56]. Moreover, this meta-analysis demonstrated a beneficial safety profile of NOACs in terms of bleeding complications with a risk ratio for major haemorrhage of 0.6 (95% CI 0.4–0.9); however, it should be noted that the absolute risk of major haemorrhage in real-world daily care may be higher than reported in the randomized controlled trials which applied strict patient selection criteria [57]. Based on these results and the practical advantages of NOACs, these drugs are likely to replace VKAs as the treatment of choice for the majority of patients with PE in the future.

A potential concern with regard to the NOACs is the current unavailability of specific antidotes, although the relevance of this in clinical practice may be limited due to the lower incidence of major haemorrhage as well as the shorter half-life of these drugs compared to VKAs [50]. Moreover, specific antidotes are currently under clinical investigation and are likely to become available in the coming years. The humanized monoclonal antibody idarucizumab, which is specifically designed as an antidote for dabigatran, directly binds to dabigatran with a higher affinity than thrombin and is currently being

Table 5. Long-term anticoagulant therapy regimens.

Drug	Standard dose	Comments
VKA	*Individually based on INR*	- Target range INR: 2.0–3.0
Oral administration		
LMWH[a]	*Enoxaparin*	- Treatment of choice for cancer-associated PE for at least the first 6 months, evidence for the period beyond the first 6 months is lacking and a switch to a VKA may be considered
	1.0 mg/kg b.i.d.	
Subcutaneous injection	*1.5 mg/kg o.d.*	
	Tinzaparin	- After the first month a dose reduction to 80% of the initial dose can be considered
	175 U/kg o.d.	- Contraindicated if creatinine clearance <30 mL/min
	Nadroparin	
	86 IU/kg b.i.d.	
	171/kg o.d.	
Dabigatran[a]	150 mg b.i.d.	- At least 5 days combined with a direct-action anticoagulant therapy (i.e. LMWH)
Oral administration		- Almost completely renal clearance
		- Contraindicated if creatinine clearance <30 mL/min
Rivaroxaban[a]	20 mg b.i.d.	- First 3 weeks, a higher dose of 15 mg b.i.d.
Oral administration		- Contraindicated if creatinine clearance <30 mL/min
Apixaban[a]	5 mg b.i.d.	- First 7 days, a higher dose of 10 mg b.i.d.
Oral administration		- Contraindicated if creatinine clearance <25 mL/min
Edoxaban[a]	60 mg o.d.	- At least 5 days combined with a direct-action anticoagulant therapy (i.e. LMWH)
Oral administration		- Contraindicated if creatinine clearance <30 mL/min

Note: VKA, vitamin K antagonist; LMWH, low molecular weight heparin; b.i.d., twice daily; o.d., once daily; INR, international normalized ratio; PE, pulmonary embolism. [a]Approval may vary between countries.

tested in a phase III trial (NCT02104947). Andexanet alpha is a recombinant modified form of factor Xa that directly binds factor Xa inhibitors without procoagulant activity and is a potential universal antidote for the anti-Xa inhibitors as well as for LMWH. Two phase III trials have recently been initiated to evaluate the effects of andaxanet alpha in healthy volunteers (NCT02220725, NCT02207725) and a study in patients with a major haemorrhage whilst treated with a factor Xa inhibitor is planned (NCT02329327).

For the specific category of patients with cancer-associated PE, long-term LMWHs are the treatment of choice for at least the first 6 months of therapy, based on a higher efficacy [hazard ratio (HR) of recurrent VTE 0.48; 95% CI 0.30–0.77] in combination with a comparable risk of bleeding complications compared to VKA treatment [58]. Although a meta-analysis of patients with cancer included in the NOAC trials suggested a favourable efficacy and similar safety profile compared to VKAs, dedicated clinical trials comparing these drugs to LMWHs in patients with cancer are required [59]. Therefore, at present, NOACs cannot be recommended for the treatment of cancer-associated VTE. Finally, an inferior vena cava filter is a temporary alternative for patients with an absolute contraindication to anticoagulant therapy [7].

Long-term anticoagulant therapy (after the first 3 months)

To determine the optimal duration of treatment after the initial 3 months, the perceived risk of anticoagulant therapy-associated haemorrhage should be weighed against the risk of recurrent VTE in every patient individually.

It has been estimated that the risk of major haemorrhage after the initial 3 months of therapy is 2.74 per 100 patient-years, but the risk can vary widely depending on patient characteristics [60]. Known risk factors for bleeding complications are older age, previous gastrointestinal bleeding, previous stroke, chronic renal or liver disease, alcohol abuse, concomitant antiplatelet therapy, presence of serious comorbidities and poor control of anticoagulant therapy [7]. Several clinical prediction rules derived in patients with VTE as well as those derived and validated in patients with atrial fibrillation have been investigated. However, none of these prediction rules is currently validated to use in daily clinical practice as a result of low reproducibility, a low c-statistic indicating a limited predictive value and/or the lack of validation studies [61]. Moreover, it should be noted that the case-fatality rate of anticoagulant therapy-associated major haemorrhage (13.4%; 95% CI 9.4–17.4) has been reported to be higher than that of recurrent VTE (3.6%; 95% CI 1.9–5.7), and therefore, the clinical impact of major haemorrhage may be considered to be higher than that of recurrent VTE [49, 60].

Regarding the risk of recurrent VTE, it should be emphasized that extending the duration of anticoagulant therapy only postpones a potential recurrent VTE without diminishing the VTE recurrence risk after anticoagulant therapy is stopped [62]. In patients with PE related to a transient provoking factor (e.g. recent surgery, immobilization, pregnancy or oral contraceptive use), a recurrence risk of approximately 2.5% per year is usually considered low enough to discontinue anticoagulant therapy after 3 months [7, 47]. On the other hand, the recurrence risk in patients with an active malignancy (20.7% during the first 12 months of therapy) [63], the antiphospholipid syndrome [64] or a previous episode of VTE (20.7% after 4 years of follow-up after initial 6 month therapy) [65] is considered to be high enough for guidelines to suggest that these patients should be treated for an extended or indefinite duration [7].

Because most recurrences occur shortly after cessation of anticoagulant therapy, it has been proposed that patients with a second VTE that occurred after a long interval following the first VTE may have a relatively low recurrence risk and therefore may benefit from a limited duration of treatment. However, in a recent cohort study, the incidence rate of a third VTE after an interval of >1 year following cessation of treatment for the first VTE was 12 per 100 patient-years (95% CI 7.4–19.0) and 5.6 per 100 patient-years (95% CI 2.2–12.0) in patients with an unprovoked and a provoked second VTE, respectively [66]. Therefore, differentiation based on the interval between the first and second VTE cannot be recommended for patients with an unprovoked second VTE, whereas a limited duration of treatment can be considered in patients with a provoked second VTE.

In patients with a first unprovoked PE not associated with cancer or the antiphospholipid syndrome, which is associated with a recurrence risk of at least 4.5% per year, determining the optimal duration of treatment is usually more complicated. Standard screening for inherited and acquired thrombophilia is not recommended as studies have failed to demonstrate a benefit and the predictive value for a recurrent VTE of most thrombophilic factors is relatively low [67]. Measuring the D-dimer level as a general marker of coagulation activity may be valuable for predicting the recurrence risk, although results from prospective studies were inconsistent with incidence rates varying from 3.0% to 6.7% per year after anticoagulant therapy was stopped in patients with repeated negative D-dimer test results [68, 69]. The Vienna prediction model is a recently externally validated nomogram consisting of the variables sex, location of the VTE and the D-dimer concentration and is currently being evaluated in a prospective management study [70, 71]. In this ongoing study, patients with a low-risk score (<180 points; expected 12-month recurrence risk 4.4%; 95% CI 2.7–6.2) receive anticoagulant therapy for 3–7 months, whilst therapy is continued in the remaining patients (NCT01972243). The "men continue and HER DOO2 prediction rule" consists of four variables: post-thrombotic signs, D-dimer concentration of ≥250 µg/L (whilst on anticoagulant therapy), body mass index ≥30 kg/m^2 and age ≥60 years. In an observational study, this score differentiated between a low-risk category with an annual risk of 1.6% (≤1 point; 95% CI 0.3–4.6) and a higher-risk group with an annual risk of 14.1% (≥2 points; 95% CI 10.9–17.3) only in women and is currently being investigated in a prospective management study (NCT00967304) [72]. Finally, the DASH score has been derived from a patient-level meta-analysis and consists of four variables: an abnormal postcoagulation D-dimer concentration, age <50 years, male sex and hormonal therapy. This score was able to differentiate between groups with an annual VTE incidence of 3.1% (95% CI 2.4–3.9) and 9.3% (95% CI 8.1–10.8) [73]. However, in the absence of results from prospective management studies, none of these scores can currently be recommended for daily clinical practice.

The major concern with the use of anticoagulant therapy for an indefinite period is the persistent risk of major haemorrhage. Therefore, alternative strategies that may be associated with a lower risk of haemorrhage have been investigated, including low-intensity VKA therapy with a target INR of 1.5–1.9 and aspirin. Low-intensity VKA therapy was less effective compared to conventional-intensity VKA therapy, with a similar risk of major haemorrhage [74]. Therefore, low-intensity VKA therapy cannot be recommended for the secondary prevention of VTE. More recently, two randomized trials have been conducted to investigate the effect of aspirin after standard anticoagulant therapy for long-term secondary VTE prevention. In the WARFASA trial, a significant reduction in VTE recurrence risk was observed from 11.2% per year for placebo to 6.6% for aspirin (OR 0.58; 95% CI 0.36–0.93), whilst the risk of major haemorrhage was similar (1/197 for

placebo vs. 1/205 for aspirin) [75]. The ASPIRE trial demonstrated only a nonsignificant decrease in the risk of VTE recurrence from 6.5% per year for placebo to 4.8% per year for aspirin (HR 0.74; 95% CI 0.52–1.05) together with a nonsignificant increase in the risk of major haemorrhage from 0.6% to 1.1% per year (HR 1.73; 95% CI 0.72–4.11) [76]. Although these results suggest that aspirin may reduce the VTE recurrence risk, it is clear that it does not provide reliable protection against recurrent VTE in comparison with long-term oral anticoagulation. Therefore, long-term secondary prevention with aspirin is not recommended by current treatment guidelines, although it may be considered as an alternative for extended treatment in patients who are unable to tolerate any type of oral anticoagulants [77].

The effects of dabigatran, apixaban and rivaroxaban on long-term secondary prevention after initial management for VTE (either DVT or PE) have also been investigated. Only dabigatran has been compared to warfarin and was shown to be noninferior (HR 1.44; 95% CI 0.78–2.64) for recurrent VTE with a nonsignificantly lower risk of major haemorrhage (HR 0.52; 95% CI 0.52–1.02) [78]. As expected, dabigatran was more effective than placebo (HR 0.08; 95% CI 0.02–0.25), whilst major haemorrhage occurred in only two of 684 patients (0.3%) versus none of 659 patients receiving placebo. Two doses of apixaban (2.5 and 5 mg twice daily) were compared to placebo for a period of 12 months after initial treatment [79]. These doses of apixaban were shown to be similarly effective with a recurrence risk of 1.7% in both groups compared to 8.8% in patients who received placebo. Remarkably, both doses were not associated with a higher risk of major haemorrhage compared to placebo. Finally, rivaroxaban for an additional 6–12 months after initial treatment demonstrated superior efficacy compared to placebo (8/602 vs. 42/594; HR 0.18; 95%CI 0.09-0.39) for recurrent VTE, whilst nonfatal major haemorrhage occurred in only four of 598 patients (0.7%) treated with rivaroxaban [80]. Although all studies were performed in highly selected groups of patients who completed initial therapy without complications and only dabigatran has been compared to VKA therapy, these findings together with the results from initial management studies suggest that NOACs are as effective as VKA therapy and have a lower risk of major haemorrhage than long-term VKA therapy. Therefore, the introduction of NOACs is likely to change the risk–benefit ratio of long-term anticoagulant therapy and may influence clinicians to extend the duration of treatment more often in selected patient groups.

CONCLUSIONS

The standardized diagnostic management of clinically suspected acute PE allows the exclusion of PE without imaging tests in approximately 30% of patients; this proportion can be further increased using the recently validated age-adjusted D-dimer threshold.

Future studies should focus on further limiting the number of required imaging tests as well as improving the implementation of standardized management in daily clinical practice, as nonadherence decreases safety and efficiency.

PE management is becoming increasingly more stratified by developing criteria to select patients who can be safely treated in the outpatient setting, and thrombolytic therapy should be reserved for patients with haemodynamic instability or those with haemodynamic deterioration during the first days after the diagnosis of PE. The introduction of NOACs simplifies anticoagulant therapy and the associated risk of major haemorrhage seems to be lower than that of VKA therapy. Nevertheless, clinical prediction rules to estimate the risk of anticoagulant therapy-associated major haemorrhage as well as clinical prediction rules to estimate the risk of recurrent VTE are required to come to a more tailored long-term management of PE.

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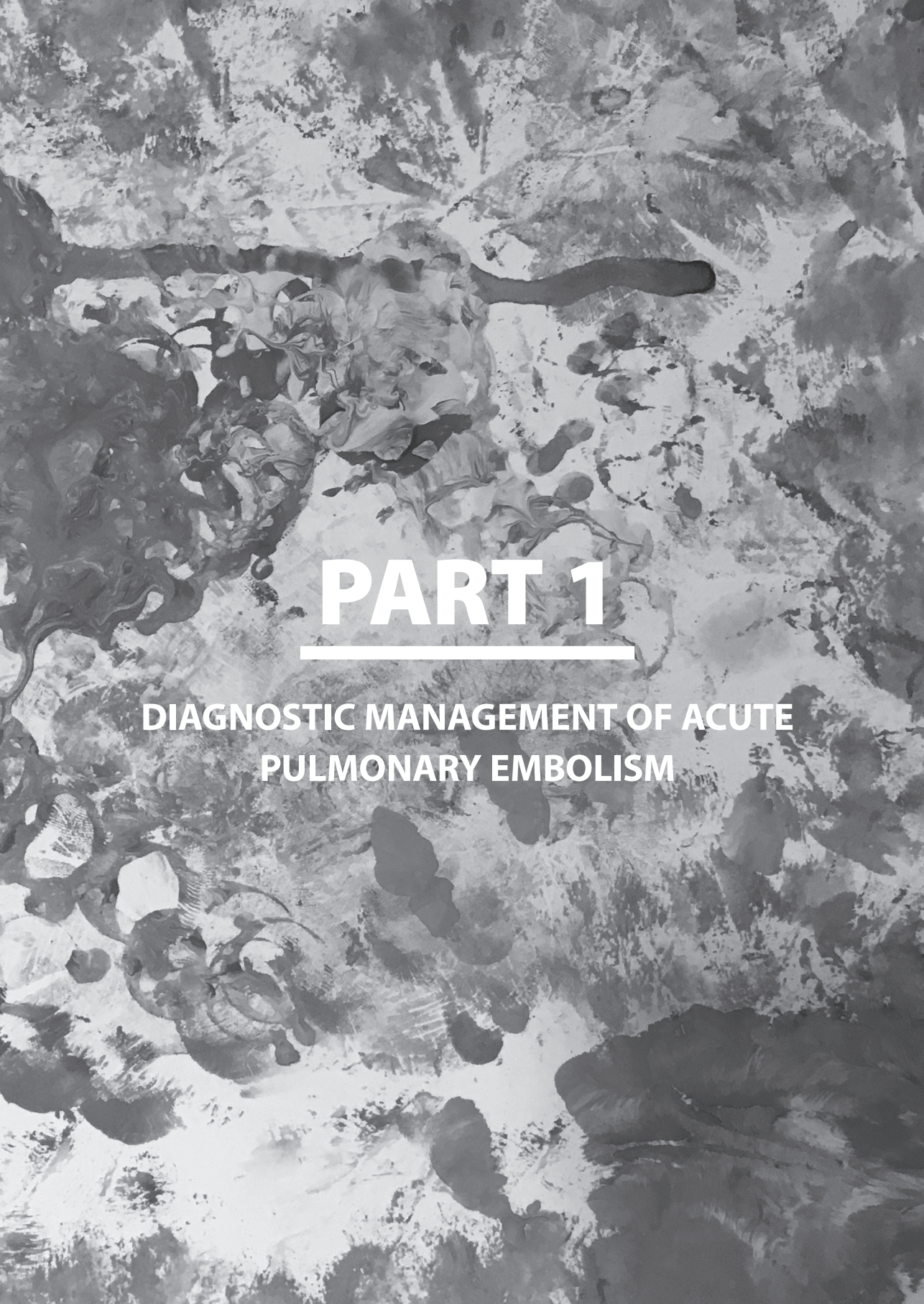

PART 1

DIAGNOSTIC MANAGEMENT OF ACUTE PULMONARY EMBOLISM

CHAPTER 3

Wells rule and D-dimer testing to rule out pulmonary embolism - a systematic review and individual-patient data meta-analysis -

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ABSTRACT

Background

The performance of different diagnostic strategies for pulmonary embolism (PE) in patient subgroups is unclear.

Purpose

To evaluate and compare the efficiency and safety of the Wells rule with fixed or age-adjusted D-dimer testing overall and in inpatients and persons with cancer, chronic obstructive pulmonary disease, previous venous thromboembolism, delayed presentation, and age 75 years or older.

Data Sources

MEDLINE and EMBASE from 1 January 1988 to 13 February 2016.

Study Selection

6 prospective studies in which the diagnostic management of PE was guided by the dichotomized Wells rule and quantitative D-dimer testing.

Data Extraction

Individual data of 7268 patients; risk of bias assessed by 2 investigators with the QUADAS-2 (Quality Assessment of Diagnostic Accuracy Studies 2) tool.

Data Synthesis

The proportion of patients in whom imaging could be withheld based on a "PE-unlikely" Wells score and a negative D-dimer test result (efficiency) was estimated using fixed (≤500 µg/L) and age-adjusted (age × 10 µg/L in patients aged >50 years) D-dimer thresholds; their 3-month incidence of symptomatic venous thromboembolism (failure rate) was also estimated. Overall, efficiency increased from 28% to 33% when the age-adjusted (instead of the fixed) D-dimer threshold was applied. This increase was more prominent in elderly patients (12%) but less so in inpatients (2.6%). The failure rate of age-adjusted D-dimer testing was less than 3% in all examined subgroups.

Limitation

Post hoc analysis, between-study differences in patient characteristics, use of various D-dimer assays, and limited statistical power to assess failure rate.

Conclusion

Age-adjusted D-dimer testing is associated with a 5% absolute increase in the proportion of patients with suspected PE in whom imaging can be safely withheld compared with fixed D-dimer testing. This strategy seems safe across different high-risk subgroups, but its efficiency varies.

INTRODUCTION

The diagnosis of pulmonary embolism (PE) cannot be based on clinical features alone because the signs and symptoms of PE are not specific [1]. Objective imaging tests, including computed tomography pulmonary angiography (CTPA), are therefore warranted to confirm or refute the presence of PE [2]. Only 15% to 25% of presenting patients have PE [3], so CTPA is not an appropriate first-line test because of radiation exposure, costs, and risk for contrast-induced nephropathy.

To guide decisions about who should be referred for imaging, various diagnostic algorithms have been developed over the past 2 decades. They aim to identify patients at low risk for PE in whom imaging and anticoagulant treatment can be safely withheld. One frequently used algorithm consists of the sequential application of the dichotomized Wells rule [4], which estimates the clinical probability of PE, and D-dimer testing. Pulmonary embolism can be considered ruled out in patients with a Wells score of 4 or less and a negative D-dimer test result (conventionally ≤500 µg/L) [5]. This combination is present in approximately 30% to 40% of those with suspected PE [3]. The latter proportion is commonly called the "efficiency" of the algorithm. The proportion of these patients with symptomatic venous thromboembolism (VTE) during 3-month follow-up (the failure rate) is less than 1% [3]. It has recently been shown that the efficiency can be safely increased by applying an age-adjusted D-dimer positivity threshold, which is defined as the age of patients multiplied by 10 µg/L in those older than 50 years [6].

Although many studies have validated the clinical utility and safety of the dichotomized Wells rule combined with D-dimer testing in excluding PE, an individual-patient data (IPD) meta-analysis can address important questions with greater precision and power. First, what is the overall efficiency and safety of the Wells rule and fixed D-dimer testing? Second, what is the performance of this strategy in clinically important subgroups? Third and most important, how do the efficiency and safety of age-adjusted D-dimer testing compare with fixed D-dimer testing?

To answer these questions, we did a systematic review and IPD meta-analysis combining patient-level data from 6 large, prospective outcome studies in which diagnostic management of clinically suspected PE had been guided by the Wells rule and D-dimer testing. Using the fixed and age-adjusted D-dimer thresholds, we estimated the efficiency and failure rate of this diagnostic algorithm overall; in inpatients; and in persons with cancer, chronic obstructive pulmonary disease (COPD), age 75 years or older, previous VTE, and delayed presentation.

METHODS

We developed a protocol (Appendix, all appendixes are available at www.annals.org) and followed the guidance of the PRISMA-IPD (Preferred Reporting Items for Systematic reviews and Meta-Analyses of individual participant data) Statement [7].

Data Sources and Searches

We searched MEDLINE and EMBASE from 1 January 1998 (the year in which the Wells score was introduced) [8] to 13 February 2016. The search was based on a previously published search strategy [3], which included terms for "pulmonary embolism" and "D-dimer", and an adapted search filter for diagnostic and prognostic studies [9]. We restricted the search to original studies in adults. No language restrictions were applied. The full search strategy is provided in Appendix Table 1. Two authors (N.E. and T.H.) independently screened the titles and abstracts of the identified articles and independently assessed the full-text articles for eligibility. Conflicts were resolved by discussion.

Study Selection

Eligible studies included those that had prospectively enrolled, consecutive, hemodynamically stable adults presenting in a secondary care setting (emergency department or inpatient ward) with signs and symptoms suggestive of acute PE. At the individual level, the clinical probability of PE had to be assessed by the Wells rule and followed by quantitative D-dimer testing in patients with a Wells score of 4 or less (indicating "PE unlikely"). According to the study protocol, patients with a PE-unlikely Wells score and a negative D-dimer test result were to be managed without imaging and anticoagulant therapy but prospectively followed for 3 months to document the occurrence of VTE (Appendix Figure). By applying these criteria, we aimed to identify all studies that prospectively evaluated the current diagnostic management of patients with suspected PE in a secondary care setting.

Data Extraction and Quality Assessment

Authors of studies fulfilling the inclusion criteria were invited to provide IPD, and all agreed. We sought study-level information on D-dimer assays used; imaging tests done to confirm PE; and definitions of the outcomes, regardless of whether outcome measures were adjudicated by an independent committee. Patient-level data collected at baseline included information on demographics, risk factors for VTE, Wells score items, D-dimer levels (converted to µg/L), and results of imaging tests. We also collected follow-up data about anticoagulant treatment for reasons other than VTE, symptomatic VTE, mortality, or loss to follow-up. We followed the subgroup definitions used in each study without any adjustments and ascertained these definitions by the case report forms of the studies and variable labels in the study databases.

Two authors who were not involved in the original studies independently assessed each study for potential sources of bias and applicability concerns using the QUADAS-2 (Quality Assessment of Diagnostic Accuracy Studies 2) tool [10].

Data Synthesis and Analysis

Our analysis focused on the efficiency and failure rate of the diagnostic strategy. Efficiency was defined as the number of patients with a Wells score of 4 or less and a negative D-dimer test result relative to the total number of patients. We evaluated the efficiency of 2 D-dimer positivity thresholds: the conventional, fixed threshold of 500 µg/L and an age-adjusted threshold, which was defined as the age of patients multiplied by 10 µg/L in patients older than 50 years. For example, the age-adjusted strategy in a patient aged 75 years would lead to a D-dimer positivity threshold of 750 µg/L. To evaluate age-adjusted D-dimer testing in our study, we reclassified patients enrolled in studies that evaluated fixed D-dimer testing according to the age-adjusted D-dimer threshold post hoc.

The failure rate was defined as the proportion of patients with symptomatic deep venous thrombosis, nonfatal PE, or fatal PE during 3-month follow-up or objectively confirmed PE at baseline that was previously ruled out on the basis of a Wells score of 4 or less and a negative D-dimer test result. Death was considered to be caused by PE if it was confirmed by autopsy, if an imaging test for PE yielded positive results just before death, or in the case of sudden death due to unknown reasons.

The efficiency and failure rates were calculated overall and in clinically important high-risk subgroups, including inpatients and patients with cancer, COPD, age 51 to 74 years, age 75 years or older, previous VTE, and symptoms lasting more than 7 days.

Statistical Analysis

To avoid bias associated with excluding missing data [11], we used multiple imputation separately within each study (10 times). The proportion of missing values is reported in Appendix Table 2. Results across the multiply imputed data sets were combined by using the Rubin rule [12] (Appendix).

A single-stage meta-analytic approach was used [13, 14] to analyze the efficiency and failure rates. The overall efficiency (the proportion of patients in whom imaging could be withheld) was estimated using a multilevel logistic regression model (also called a generalized linear mixed-effects model), with the combination of a Wells score of 4 or less and a negative D-dimer test result as the outcome variable. To account for the clustering of observations within studies, we specified a random effect for the intercept. For the analysis in subgroups, we used a full random-effects model [13] by adding the subgroup indicator as a covariate and allowing a study-specific random effect. From these models,

we calculated the marginal probabilities (with 95% CIs) of having a PE-unlikely Wells score and a negative D-dimer test result, both overall and in the different subgroups (Appendix).

Differences in efficiency between subgroups were tested by using the Wald test statistic with the significance level set at 0.05. The absolute difference in the efficiency of the fixed and age-adjusted D-dimer testing strategies was calculated by subtracting the point estimates of the marginal probabilities from the 2 models. The 95% CIs around these estimates were obtained by repeating the analyses in 500 bootstrap samples (Appendix).

Using similar methods, we estimated the failure rate: the proportion of patients with symptomatic VTE during 3-month follow-up in whom the Wells score and D-dimer test result had ruled out PE at baseline. The outcome variable in this multilevel logistic regression model was a final diagnosis of VTE. The analysis was restricted to patients with a Wells score of 4 or less and a negative D-dimer test result. Patients receiving anticoagulant treatment for reasons other than VTE and those lost to follow-up were excluded from this analysis. Failure rates in the subgroups were estimated using full random-effects models, with the subgroup indicator as the covariate. We calculated estimates of the marginal probabilities of the failure rates with 95% CIs.

Heterogeneity among the studies was assessed by calculating 90% prediction intervals around the estimates for the efficiency and failure rate based on the random intercept variance [13]. Because the proportion of missing baseline variables was higher in the REPEAD study [15] than in the other studies (from 1% for duration of symptoms to 21% for cancer) (Appendix Table 2), we did a sensitivity analysis in which REPEAD was excluded.

To better understand and illustrate the association between age and the efficiency and associated failure rate for the fixed and age-adjusted D-dimer thresholds, we extended the base models by adding age as a continuous variable. Age was then plotted against the predicted proportions from these models. This analysis was restricted to patients older than 50 years because the age-adjusted D-dimer threshold, by definition, applies only to them.

Because patients with clinically suspected PE often have more than 1 risk factor for PE, the conditional effect of the potential predictors of a difference in efficiency was also evaluated with a multilevel, multivariable, logistic regression model in which all predefined subgroup indicators were included as covariates.

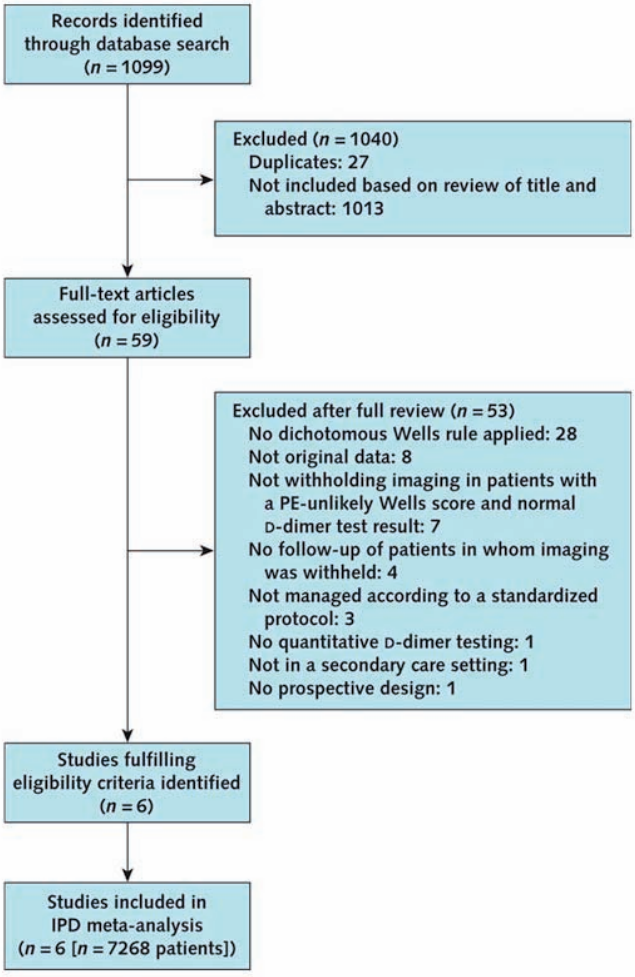
All statistical analyses were performed in R, version 3.2.2 (R Foundation for Statistical Computing; www.R-project.org), by using the mice package (version 2.22) for multiple imputation, the lme4 package (version 1.1-10) for multilevel logistic regression modeling, and the boot package (version 1.3-18) for bootstrapping. Specifications of all models used are provided in Appendix Table 3.

RESULTS

Our search identified 1099 articles, 59 of which were assessed for eligibility (**Figure 1**). Exclusion criteria are provided in Appendix Table 4. Six studies fulfilled the eligibility criteria [5, 6, 15–18], and IPD for all 7268 patients were obtained.

Basic characteristics and outcomes of the 6 included studies are summarized in **Table 1**. These studies used a diagnostic strategy consisting of the Wells rule and subsequent D-dimer testing to guide the management of patients with suspected PE. Three studies enrolled both inpatients and outpatients [5, 15, 16].

Figure 1. Systematic search and study selection.



Note: IPD: individual-patient data; PE: pulmonary embolism.

Table 1. Characteristics of Included Studies.

Study	Primary study goal	Study period	D-dimer assay	Diagnostic imaging test	Outcome adjudication	Total number of patients	Number of patients with VTE at baseline or during follow-up (%)	Number of patients managed without imaging (%)	Number of patients managed without imaging and anticoagulation with VTE during follow-up (%)
Christopher study (2006) [5]	Evaluation of Wells rule combined with D-dimer testing (threshold 500 µg/L) in in- and outpatients	November 2002 – September 2004	VIDAS or Tina-quant	CTPA	Yes	3306	700 (21%)	1057 (32%)	5 (0.5%)
Goekoop et al. (2007) [17]	Evaluation of Wells rule combined with D-dimer testing (threshold 500 µg/L) in outpatients	March 2002 – March 2004	VIDAS	CTPA or VQ-scan	No	879	110 (13%)*	450 (51%)	2 (0.4%)
Prometheus study (2008) [15]	Evaluation of 4 clinical decision rules (including dichotomized Wells rule) combined with D-dimer testing (threshold 500 µg/L) in in- and outpatients	July 2008 – November 2009	VIDAS, Tina-quant, STA Liatest, or Innovance	CTPA	Yes	807	192 (24%)	169 (21%)†	1 (0.6%)
Galipienzo et al. (2012) [18]	Evaluation of dichotomized Wells rule combined with D-dimer testing (cut-off 500 µg/L) in outpatients	May 2007 – December 2008	VIDAS	CTPA	No	241	64/241 (27%)	57 (24%)	0 (0%)
ADJUST study (2014) [6]	Evaluation of dichotomized Wells rule combined with D-dimer testing (age-adjusted cut-off) in outpatients older than 50 years	January 2010 – February 2013	VIDAS, Tina-quant, STA Liatest, D-Dimer HS or Innovance	CTPA	Yes	1753‡	345 (20%)	523 (30%)	2 (0.4%)

Table 1. Characteristics of Included Studies. (continued)

Study	Primary study goal	Study period	D-dimer assay	Diagnostic imaging test	Outcome adjudication	Total number of patients	Number of patients with VTE at baseline or during follow-up (%)	Number of patients managed without imaging (%)	Number of patients managed without imaging and anticoagulation with VTE during follow-up (%)
REPEAD study (2014) [16]	Evaluation of dichotomized Wells rule combined with D-dimer testing (cut-off 500 µg/L) in in- and outpatients with previous PE	November 2002 – November 2009	VIDAS, Tina-quant, STA Liatest, or Innovance	CTPA	Yes	282‖	117 (42%)	47 (17%)	0 (0%)

Note: CDR: clinical decision rule; CTPA: computed tomography pulmonary angiography; PE: pulmonary embolism; VQ: ventilation-perfusion scan

* Follow-up was not planned for patients with a Wells score >4 points or with the combination of a Wells score ≤4 points and a negative D-dimer (threshold 500 µg/L).

† Patients were managed without imaging when all 4 clinical decision rules classified the patient as "PE unlikely" combined with a negative D-dimer (threshold 500 µg/L).

‡ Individual patient data was obtained only from patients that were assessed with the Wells rule.

‖ Patients that were enrolled both in the Christopher and REPEAD studies were excluded from the analysis.

Subgroup definitions were homogeneous across the studies. The definitions of cancer and previous VTE followed those as per the Wells score in all studies. Chronic obstructive pulmonary disease was defined as disease requiring treatment in 4 of 5 studies that captured this variable and as disease with or without treatment in one. The fixed D-dimer threshold of 500 µg/L was applied in 5 studies, whereas the age-adjusted D-dimer threshold was used in one. D-Dimer testing was done using the locally available method: a quantitative latex-based assay or an enzyme-linked immunosorbent assay. In each study, imaging and anticoagulant therapy were withheld in patients with a Wells score of 4 or less and a negative D-dimer test result. They were followed prospectively for 3 months by telephone contact or a scheduled outpatient visit.

We identified potential sources of bias. Suspected venous thromboembolic events during 3-month follow-up were not centrally adjudicated in 2 studies [17, 18]. Quantitative D-dimer testing was not done in 104 of 5202 patients (2.0%) with a Wells score of 4 or less, and 11 patients (0.4%) in whom imaging was withheld at baseline were lost to follow-up. In all studies, the risk of bias with respect to patient selection, Wells scores, and D-dimer test results was judged to be low. Of note, concern for limited applicability in all domains was low (complete QUADAS-2 results are provided in the appendix).

Baseline patient characteristics are summarized in Appendix Table 5. The mean age was 56 years; 42% were men. The proportion of missing values for the baseline characteristics and Wells score items ranged from 0% to 6%. Among patients across the studies with a PE-unlikely Wells score, 0% to 10% had missing quantitative D-dimer test results. When we checked the IPD, no other concerns were identified. At baseline, PE was diagnosed in 1527 patients (21%).

The overall efficiency of the diagnostic strategy when the fixed D-dimer threshold of 500 µg/L was applied was 28% (95% CI, 21% to 37%) (**Table 2**). The summary estimate of the failure rate was 0.65% (CI, 0.38% to 1.11%) (**Table 3**), without any fatal events, among patients with a PE-unlikely Wells score and a negative D-dimer test result (without imaging). Five percent of patients with a PE-unlikely Wells score had D-dimer levels between 500 µg/L and the age-adjusted threshold. This resulted in an overall efficiency of 33% (CI, 25% to 42%) when the age-adjusted D-dimer threshold was applied. The failure rate among patients in whom imaging was withheld based on a Wells score of 4 or less and a D-dimer level below the age-adjusted threshold was 0.94% (CI, 0.58% to 1.5%), with 1 fatal event.

The efficiency of the diagnostic algorithms in the prespecified subgroups of patients is presented in **Table 2**. When the fixed D-dimer threshold is applied, the efficiency varied from 7% in inpatients to 25% in persons having symptoms for more than 7 days. The efficiency of age-adjusted D-dimer testing varied from 10% in inpatients to 32% in persons with COPD. Compared with fixed D-dimer testing, age-adjusted testing increased the efficiency ranging from 12% in elderly patients to 2.6% in inpatients.

Table 2. Efficiency* of the Wells Rule and D-Dimer Testing in Excluding PE Overall and in Clinically Important Subgroups.

		Active cancer		Chronic obstructive pulmonary disease		Age			Previous venous thromboembolism		Duration of symptoms		Hospitalization status	
	Overall (n=7,268)	Yes n=938)	No (n=6,264)	Yes (n=856)	No (n=6,017)	≥ 75 years (n=1,200)	51-74 years (n=3,398)	≤ 50 years (n=2,661)	Yes (n=1,116)	No (n=6,143)	> 7 days (n=1,322)	≤ 7 days (n=5,476)	Inptient (n=804)	Outpatient (n=6,455)
D-dimer threshold 500 µg/L, %	28.0	9.1	30.4	21.3	29.8	8.4	22.4	45.1	16.5	31.9	25.2	29.9	7.0	30.1
95% CI	20.5-37.0	6.8-12.0	23.0-39.1	16.6-26.8	20.2-41.5	6.3-11.0	17.5-28.2	34.9-55.7	13.8-19.6	23.5-41.6	16.8-35.8	20.8-40.6	2.5-17.3	22.4-39.1
90% PI	14.3-47.4	4.3-18.3	16.7-48.6	9.7-40.2	12.8-54.5	2.6-23.9	10.9-40.1	25.8-65.9	9.3-27.4	16.9-51.6	8.3-54.6	13.8-52.7	1.3-27.6	15.9-49.3
Age-adjusted D-dimer threshold, %	32.6	13.1	35.2	31.5	33.4	20.3	28.0	45.1	19.0	36.9	29.7	34.1	9.9	34.7
95% CI	24.6-41.7	10.6-16.1	27.3-43.9	26.5-37.0	23.2-45.2	15.9-25.5	20.7-36.5	34.7-55.8	16.4-21.8	28.7-45.8	21.1-39.9	24.5-45.2	5.3-17.4	26.8-43.5
90% PI	17.8-51.8	7.4-22.1	20.4-53.3	16.8-51.1	15.2-57.9	7.6-43.9	14.0-47.6	25.7-66.0	12.1-28.4	22.1-54.4	11.3-57.9	16.7-56.9	2.7-28.8	19.9-52.9
Absolute increase in efficiency, %	4.6	3.8	4.7	10.2	3.6	12.1	5.6	0	2.5	5.2	4.6	4.2	2.6	4.6
95% CI	4.3-4.8	3.1-4.4	4.5-5.0	9.4-10.9	3.4-3.7	11.4-12.7	5.2-6.2	NA	2.0-2.9	4.8-5.7	4.2-5.0	4.0-4.4	1.9-3.1	4.4-4.8

Note: CI: confidence interval; PI: prediction interval.

*The efficiency is defined as the probability of having an unlikely Wells score combined with a negative D-dimer test result. All subgroup differences (e.g. cancer vs. no cancer) were statistically significant (P<0.05), except for chronic obstructive pulmonary disease in the analysis of age-adjusted D-dimer testing (P=0.89).

Table 3. Failure Rate* of the Wells Rule and D-Dimer Testing in Excluding PE Overall and in Clinically Important Subgroups.

		Active cancer		Chronic obstructive pulmonary disease		Age			Previous venous thromboembolism		Duration of symptoms		Hospitalization status	
	Overall (n=7,268)	Yes (n=938)	No (n=6,264)	Yes (n=856)	No (n=6,017)	≥ 75 years (n=1,200)	51-74 years (n=3,398)	≤ 50 years (n=2,661)	Yes (n=1,116)	No (n=6,143)	> 7 days (n=1,322)	≤ 7 days (n=5,476)	Inpatient (n=804)	Outpatient (n=6,455)
D-dimer threshold 500 µg/L	0.65	2.6	0.57	0.74	0.64	NA	NA	NA	1.3	0.56	0.88	0.62	NA	NA
95% CI	0.38-1.11	0.57-11.0	0.31-1.0	0.11-4.7	0.37-1.1	NA	NA	NA	0.12-13.3	0.29-1.1	0.28-2.7	0.33-1.1	NA	NA
90% PI	0.42-0.99	0.77-8.3	0.36-0.91	0.15-3.5	0.40-1.0	NA	NA	NA	0.16-10.0	0.33-0.95	0.34-2.2	0.37-1.0	NA	NA
Age-adjusted D-dimer threshold	0.94	1.4	0.89	1.2	0.90	2.1	0.83	0.59	1.2	0.90	1.3	0.87	1.2	0.93
95% CI	0.58-1.5	0.15-12.6	0.57-1.4	0.03-25.3	0.54-1.5	0.71-5.9	0.15-4.3	0.22-1.6	0.12-11.6	0.56-1.4	0.53-3.1	0.44-1.7	0.17-8.1	0.61-1.4
90% PI	0.64-1.4	0.21-9.3	0.62-1.3	0.03-23.5	0.57-1.4	0.81-5.2	0.22-3.1	0.26-1.3	0.18-7.8	0.62-1.3	0.81-2.1	0.40-1.9	0.26-0.54	0.67-1.3

Note: CI: confidence interval; COPD: chronic obstructive pulmonary disease; PI: prediction interval; VTE: venous thromboembolism.

*The failure rate is defined as the probability of VTE in patients with an Wells score <=4 combined with a negative D-dimer test result.

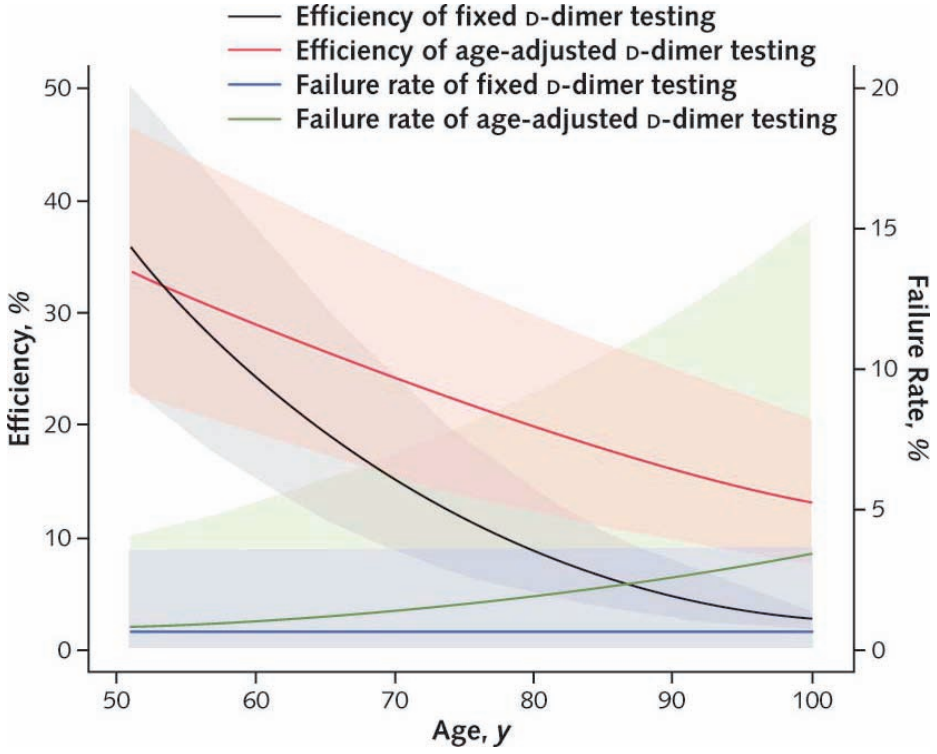
Patients who received anticoagulants for other reasons than VTE and those lost to follow-up were excluded from this analysis. The failure rate could not be estimated in the age subgroups and in inpatients when applying the fixed D-dimer threshold due to zero events.

The failure rate of the diagnostic algorithms was greatest in patients with active cancer (2.6% [CI, 0.57% to 11.0%] when the fixed D-dimer threshold is applied) and those aged 75 years or older (2.1% [CI, 0.71% to 5.9%] when the age-adjusted D-dimer threshold is applied) (**Table 3**). However, none of these subgroup differences reached statistical significance.

In the sensitivity analysis in which the REPEAD study was excluded because of a relatively higher proportion of missing baseline variables, the point estimates for efficiency were slightly higher than in the main analysis owing to the high PE prevalence and low efficiency in REPEAD (Appendix Table 6). The sensitivity analysis yielded similar results to the main analysis with respect to the failure rates (Appendix Table 7). In the exploratory analysis, the absolute difference in efficiency between the age-adjusted and fixed D-dimer thresholds increased with age from approximately 4% in patients aged 60 years to 11% in patients aged 80 years, whereas the difference in failure rate increased from 0.4% in patients aged 60 years to 1.3% in patients aged 80 years (**Figure 2**).

In the multivariable analysis, all risk factors, except COPD status, were significantly associated with a lower chance of ruling out PE based on the Wells rule and fixed D-dimer

Figure 2. Association between age and the efficiency and failure rate of the Wells rule and D-dimer testing using the fixed or age-adjusted thresholds.



testing (Appendix Table 8). Strong predictors of limited efficiency were age 75 years or older (adjusted odds ratio [OR], 0.12), inpatient status (adjusted OR, 0.21), and active cancer (adjusted OR, 0.30). In these 3 subgroups, the adjusted ORs for a Wells score of 4 or less and a D-dimer level below the age-adjusted threshold were 0.33, 0.24, and 0.34, respectively.

DISCUSSION

This large IPD meta-analysis of 7268 patients with clinically suspected PE shows that the proportion of those managed without imaging and who have no need for anticoagulation can be safely increased from 28% to 33% by applying the age-adjusted D-dimer threshold in those with a PE-unlikely Wells score. This absolute increase is more prominent in patients with COPD and elderly patients presenting with suspected PE but is less prominent in inpatients or patients with cancer, previous VTE, or delayed presentation.

A strength of our study is that it includes IPD from many persons with clinically suspected PE, which enabled robust subgroup analysis. In addition, our results pertain to the current evidence-based standards of the diagnostic management of PE [2, 19] because all patients were managed prospectively according to a widely used, uniform, and well-validated algorithm. This homogeneity in design of the included studies increased the precision of the efficiency and safety outcomes.

Our results are based in part on post-hoc analyses. The age-adjusted D-dimer threshold had been prospectively evaluated in only one study [6], whereas the efficiency and failure rate associated with this threshold were recalculated for the other studies. Therefore, we have failure rates defined from both imaging and follow-up that are not fully interchangeable. As a consequence, we may have overestimated the failure rate because most patients with a Wells score of 4 or less and a D-dimer level between the fixed and age-adjusted thresholds had imaging, which may have led to the detection of clots with less clinical significance [20].

We observed considerable between-study heterogeneity as illustrated by the relatively wide prediction intervals around the estimates. Because the included studies had a similar design, this heterogeneity was most likely due to differences in the patient population and, as a consequence, between-study differences in PE prevalence.

On average, 22% of the patients in our analysis had confirmed PE, which is substantially higher than proportions reported in most North American studies [21–23]. Therefore, the efficiency will likely be greater in settings with a lower PE prevalence. We restricted inclusion to studies conducted in secondary care; therefore, caution is warranted when extrapolating our results to, for example, primary care.

Various D-dimer assays were used in the studies. Although these widely available quantitative latex-based and enzyme-linked immunosorbent assays have a high sensitivity for diagnosing PE, their specificity may be somewhat different [24]. At present, evidence on the performance of the age-adjusted threshold with each assay is lacking [25]. Because patient-level information on the D-dimer testing method was not available for most studies, we could not compare the performance of the 2 assays. Yet we believe that this use of different D-dimer assays reflects clinical practice.

Overall, our findings are in line with previous studies that evaluated the performance of the age-adjusted D-dimer threshold. In a retrospective analysis by Douma and colleagues [26], the age-adjusted D-dimer threshold was associated with a 5% to 6% absolute increase in efficiency in the 3 cohort studies not included with the present analysis. Similarly, in a post hoc analysis of 3 cohort studies, Penaloza and colleagues [27] found a 4.6% absolute increase in the proportion of patients with a low or moderate pretest probability and a negative D-dimer test result when the age-adjusted threshold was applied. The 5% overall increase in efficiency in our study was not offset by an increase in the failure rate. Hence, when the age-adjusted (instead of the fixed) D-dimer threshold is used in clinical practice, it is expected that PE can be safely ruled out in an additional 1 of 20 patients.

This meta-analysis supports the findings of previous evaluations of the performance of clinical decision rules in combination with D-dimer testing in subgroups of patients with clinically suspected PE. We now know that such a diagnostic algorithm can safely rule out PE in patients with cancer [28, 29], COPD [30], age 76 years or older [30, 31], previous VTE [32, 33], and delayed presentation [34] as well as inpatients [31, 35]. However, the algorithm is less efficient in these subgroups than in the general population presenting with suspected PE. In most of these subgroups, the efficiency can be increased to more than 10% by applying the age-adjusted D-dimer threshold, which corresponds to a number needed to test of fewer than 10 patients to withhold 1 CTPA. For inpatients only, the efficiency of the diagnostic algorithm remains poor (10%). This is supported by the multivariate analysis, which indicated that inpatient status is the strongest predictor of a low efficiency when the age-adjusted D-dimer threshold is applied.

It is widely accepted that a diagnostic strategy for PE is considered safe if a failure rate of 3% can be excluded based on the upper limit of the 95% CI because even pulmonary angiography cannot detect all cases [36]. In our analysis, the point estimate of the failure rate was less than 3% across all subgroups and we found no evidence for a difference in failure rate between the subgroups. The statistical power was limited because of the low number of events, which was also reflected by the wide CIs.

On the basis of this analysis, we recommend using age-adjusted (rather than fixed) D-dimer testing with the Wells rule because it increases efficiency without jeopardizing safety in all studied subgroups. The improved efficiency is most pronounced in patients

with COPD and elderly patients and is considerable in those with cancer, previous VTE, or a delayed presentation. Although age-adjusted D-dimer testing increases the efficiency among inpatients from 7% to 10%, its clinical utility in this subgroup remains limited given the corresponding number needed to test of 10 patients to withhold 1 CTPA. Whether to rely on the Wells rule and D-dimer testing in these patients becomes a matter of judgment. It may still be valuable to avoid the risk for contrast-induced nephropathy in ill patients who often already have multiple comorbidities; however, based on the clinical presentation, physicians may decide to proceed to imaging directly without calculating a Wells score or ordering D-dimer testing.

Among patients with clinically suspected PE, the Wells rule combined with age-adjusted D-dimer testing is associated with a 5% absolute increase in the proportion of those in whom imaging can be safely withheld compared with fixed D-dimer testing. This diagnostic approach seems to be safe across various subgroups, but its clinical utility may be limited for some, particularly inpatients.

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CHAPTER 4

Is a normal computed tomography pulmonary angiography safe to rule out acute pulmonary embolism in patients with a likely clinical probability?
- a patient-level meta-analysis -

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ABSTRACT

Introduction

A normal computed tomography pulmonary angiography (CTPA) remains a controversial criterion for ruling out acute pulmonary embolism (PE) in patients with a likely clinical probability. We set out to determine the risk of VTE and fatal PE after a normal CTPA in this patient category and compare these risks to those after a normal pulmonary angiogram of 1.7% (95%CI 1.0-2.7%) and 0.3% (95%CI 0.02-0.7%).

Methods

A patient-level meta-analysis from 4 prospective diagnostic management studies that sequentially applied the Wells rule, D-dimer tests and CTPA to consecutive patients with clinically suspected acute PE. The primary outcome was the 3-month VTE incidence after a normal CTPA.

Results

A total of 6,148 patients were included with an overall PE prevalence of 24%. The 3-month VTE incidence in all 4,421 patients in whom PE was excluded at baseline was 1.2% (95%CI 0.48-2.6) and the risk of fatal PE was 0.11% (95%CI 0.02-0.70). In patients with a likely clinical probability the 3-month incidences of VTE and fatal PE were 2.0% (95%CI 1.0-4.1%) and 0.48% (95%CI 0.20-1.1%) after a normal CTPA. The 3-month incidence of VTE was 6.3% (95%CI 3.0-12) in patients with a Wells rule >6 points.

Conclusion

This study suggests that a normal CTPA may be considered as a valid diagnostic criterion to rule out PE in the majority of patients with a likely clinical probability, although the risk of VTE is higher in subgroups such as patients with a Wells rule >6 points for which a closer follow-up should be considered.

INTRODUCTION

Signs and symptoms of pulmonary embolism (PE) are highly variable and non-specific. As a result, PE is frequently considered, while in only approximately one fifth of patients the diagnosis is confirmed [1-3]. PE can only be demonstrated by an imaging test. This test, nowadays, is usually computed tomography pulmonary angiography (CTPA) due to several advantages over other imaging tests, i.e. widespread availability, small proportion of inconclusive test results, fast acquisition time and the possibility of establishing an alternative diagnosis [4, 5]. Disadvantages of CTPA include radiation exposure, risk of contrast-induced nephropathy or allergic reactions, unsuspected findings and increased healthcare costs [6, 7].

In order to reduce the need for imaging tests for suspected PE, diagnostic algorithms have been developed for patients with suspected PE without shock or hypotension, starting with a validated clinical decision rule (CDR) to predict the clinical probability for PE, followed by a quantitative D-dimer test and/or a CTPA [8]. In patients with a low, moderate or unlikely clinical probability according to a validated CDR (either the Wells score or the revised Geneva score) and a D-dimer concentration ≤500 μg/L or equal or below the age-adjusted D-dimer threshold in patients older than 50 years, PE can be safely excluded without further imaging tests in approximately one third of all patients [3, 9, 10]. In the remaining patients with either an unlikely clinical probability in combination with an elevated D-dimer concentration or a high or likely clinical probability CTPA is indicated [8]. This diagnostic strategy has been demonstrated to be safe with a 3-month venous thromboembolism (VTE) incidence of 0.34% (95% confidence interval (95%CI) 0.036-0.96%) in patients managed without CTPA and 1.2% (95%CI 0.8-1.8) in patients in whom PE was ruled out by CTPA [4, 11]. Importantly, it has been demonstrated that performing compression ultrasonography (CUS) of the lower extremities after a normal CTPA to rule out deep vein thrombosis (DVT) does not further diminish the risk of VTE during follow-up [4, 12-14]. Consequently, in daily clinical practice a normal CTPA alone is usually considered to be a valid diagnostic criterion to exclude PE [1-3, 15].

However, evidence on the safety of ruling out PE based on a normal CTPA in the subset of patients with a likely clinical probability of PE remains controversial. In the single post-hoc analysis of the Christopher study that investigated this issue, the 3-month VTE incidence after a negative CTPA was 1.7% (9 VTE events in 545 patients; 95%CI 0.9-3.1) in patients with a likely clinical probability compared to 0.7% (5 VTE events in 721 patients; 95%CI 0.3-1.6) in patients with an unlikely clinical probability (p-value for difference = 0.11) [1, 16]. Due to the limited evidence, in the recent guideline of the European Society of Cardiology (ESC) on the diagnosis and management of acute pulmonary embolism regarding ruling out PE in patients with a likely clinical probability are somewhat inconsistent [8]. In this ESC guideline, a class IIa recommendation (level of evidence: B) is

included stating that a normal CTPA may safely exclude PE in patients with a likely clinical probability, while in another paragraph a normal CTPA alone is recommended as a controversial criterion to rule out PE and further testing should be considered. Notably, the guideline does not provide any recommendation on which additional diagnostic strategy should be considered in case of a normal CTPA.

In order to address this issue, we evaluated the risk of VTE and fatal PE after a normal CTPA in patients with a likely clinical probability of PE by performing a patient-level meta-analysis of four large diagnostic management studies.

METHODS

Patients

Patient-level data were obtained from 4 previously published multicentre prospective diagnostic management studies of patients with clinically suspected acute PE, i.e. the Christopher study, the Prometheus study, the REPEAD study and the ADJUST-PE study [1-3, 15]. These studies were performed by our own collaboration network of several academic and non-academic hospitals in the Netherlands and had a highly comparable design as well as definition and assessment of outcomes. Also, the data of all studies are of high quality with nearly complete baseline and follow-up assessment. Study details are provided in Appendix A, available at https://th.schattauer.de. In all 4 studies, hemodynamically stable, predominantly outpatients with suspected acute PE were included. Exclusion criteria were age <18 years, treatment with therapeutic doses of anticoagulant treatment for >24 hours, life expectancy <3 months, pregnancy, a contra-indication for CTPA (i.e. allergy to intravenous contrast agents, renal insufficiency) and logistic reasons such as unavailability of CTPA, patient too ill to undergo CTPA, geographic inaccessibility precluding follow-up. In the Prometheus study, a history of PE was an additional exclusion criterion, and in the REPEAD study only patients with a history of PE were included. From the ADJUST-PE study, we only included patients from participating hospitals in the Netherlands who were all managed by the Wells score in the present analysis.

In all studies, an identical diagnostic management algorithm was used starting with the Wells CDR followed by quantitative D-dimer testing and/or CTPA, depending on the result of the Wells score. PE was excluded in case of an unlikely clinical probability (Wells score ≤4 points) in combination with a negative D-dimer test result. In the Christopher study, the Prometheus study and the REPEAD study a D-dimer threshold of 500 µg/L was used, whereas in the ADJUST-PE study the age-adjusted D-dimer threshold was applied, calculated by multiplying the patient's age by 10 in patients 50 years or older. In patients with either a likely clinical probability (Wells score >4 points) or a positive D-dimer test result, CTPA was performed and they were managed according to the CTPA result. All

studies were approved by the institutional review boards of participating hospitals and patients provided written informed consent where relevant.

All patients were prospectively followed for 3 months for the occurrence of symptomatic VTE (i.e. PE and/or DVT). Adjudication committees evaluated all episodes of suspected VTE and deaths. In case of clinically suspected PE or DVT, objective diagnostic tests were required. In case of death, information was obtained from the hospital records. In case of clinically suspected VTE, an objective clinical test was performed including CTPA or ventilation-perfusion scintigraphy for suspected PE and compression ultrasonography for suspected DVT [9, 8, 17]. Deaths were classified as caused by PE if PE was confirmed by autopsy, if PE was demonstrated by objective testing prior to death or if PE could not be confidently excluded as a cause of death. Independent adjudication committees evaluated and adjudicated all suspected VTE and deaths during follow-up. Both objectively confirmed (non-fatal) VTE and deaths caused by PE were included as outcome events.

Objectives of present study and statistical analysis

The primary objective of the current analysis was to determine the 3-month incidence of objectively diagnosed symptomatic VTE and fatal PE after a normal CTPA in patients with a likely clinical probability of acute PE assessed by the Wells score, who were not treated with anticoagulant therapy. Secondary objectives were to determine the 3-month incidence of VTE and fatal PE after exclusion of PE in the overall patient population, in the subgroup of patients in whom PE was excluded based on an unlikely clinical probability in combination with a negative D-dimer test, and in those with an unlikely clinical probability but a positive D-dimer test. For all analyses, only patients in whom PE was excluded at baseline, who did not receive anticoagulant treatment, and who were not lost to follow-up were included.

In addition, the original 3-level diagnostic algorithm was investigated in a post-hoc analysis, in which 3 different clinical probability categories are identified: a low (Wells score <2 points), an intermediate (Wells score 2-6 points) and a high clinical probability (Wells score >6 points) category [18]. By using this original diagnostic algorithm, PE is excluded without imaging test in case of a D-dimer concentration ≤500 µg/L in combination with a low or moderate clinical probability, while CTPA is indicated in the remaining patients. This analysis was performed since the recent ESC guideline considers a normal CTPA alone as a controversial criterion also in patients with a high clinical probability according to the 3-level diagnostic algorithm. Finally, we explored which patient characteristics at presentation were associated with the occurrence of VTE during 3 months of follow-up after PE was ruled out at baseline.

Patient characteristics and outcomes are reported for the total cohort and for the different clinical probability categories separately. For the purpose of this study and

to ensure comparability, we post-hoc applied the conventional D-dimer threshold of ≤500 µg/L to the patients included in the ADJUST-PE study, instead of the age-adjusted D-dimer threshold.

To estimate the 3-month VTE incidence after a normal CTPA at baseline in patients with a likely clinical probability, we used multilevel logistic regression modelling with a VTE diagnosis during follow-up as the outcome and no covariates. We specified a random effect for the intercept to account for the clustering of patients within studies. To express the 3-month VTE incidence, we estimated from this model the mean predicted 3-month probability of VTE during follow-up for patient with a likely clinical probability and a normal CTPA at baseline. Using a similar approach, we estimated the mean predicted 3-month incidence of VTE and fatal PE for the different management categories (i.e. patients with an unlikely clinical probability and a negative D-dimer test result, those with an unlikely clinical probability and an increased D-dimer but a normal CTPA, and the different management categories of the original 3-level diagnostic algorithm). D-dimer testing was not performed in a substantial proportion of patients with a Wells score of 4.5-6 points, because this test was not required by the original study protocols. We used multiple imputation to replace missing values within each study, 10 times and estimates were pooled across the imputed datasets using Rubin's rule [19]. Absolute numbers provided were derived from one of the imputed datasets.

The 3-month VTE incidence in the different management categories was compared to the 3-month VTE incidence of 1.7% (95%CI 1.0-2.7) and the incidence of fatal PE of 0.3% (95%CI 0.02-0.7) reported after a normal pulmonary angiography, traditionally the gold standard in PE diagnosis [20]. Consequently, we consider a strategy to be safe in case of a 3-month incidence of VTE and fatal PE that are equal or below these outcomes after a normal pulmonary angiography. In order to determine whether patient characteristics were associated with the occurrence of VTE during follow-up after a normal CTPA in patients with a likely clinical probability, odds ratios (OR) with 95%CI were calculated comparing patients without VTE during follow-up to those who developed VTE during follow-up using logistic regression analyses. An association was considered to be statistically significant in case of a P-value below 0.05. All statistical analyses were performed in R version 3.2.0, in particular using the *mice* and *lme4* packages (R foundation for Statistical Computing, www.R-project.org).

RESULTS

Study characteristics

The four studies available for the present analysis concerned a total of 7,975 patients. From the REPEAD study, 234 patients were overlapping with the Christopher or Pro-

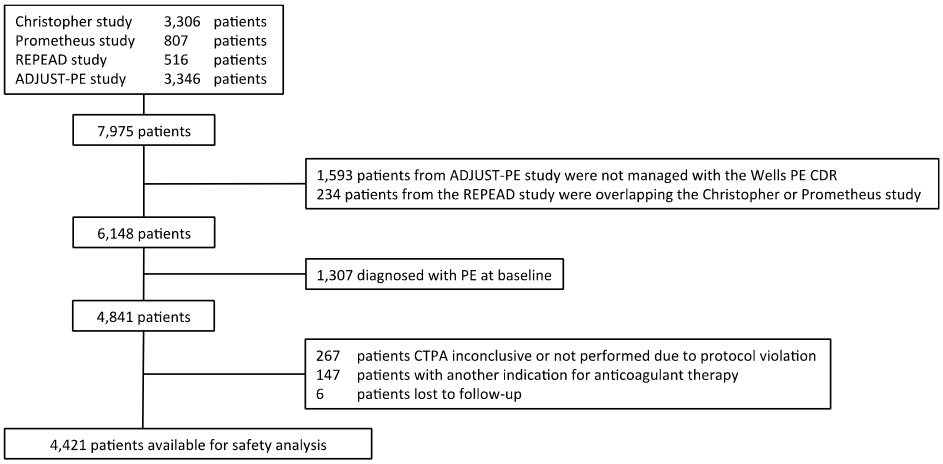
metheus study and therefore excluded from the present analysis. From the ADJUST-PE study, we included only the 1,753 patients from Dutch hospitals in whom the Wells PE CDR was used, leaving 6,148 patients with clinically suspected acute PE available for the present analysis (**Table 1**). Baseline characteristics for the individual studies are provided in Appendix B (available at https://th.schattauer.de). The PE prevalence at baseline varied from 19% to 39% between the four studies and the corresponding mean predicted PE prevalence at baseline was 24% (95%CI 18-32). In 267 patients (4.3%) CTPA was inconclusive or not performed although indicated; CTPA was not performed in 187 patients in the ADJUST-PE study as the result of a D-dimer concentration between the conventional and the age-adjusted D-dimer threshold; 147 patients (2.4%) received anticoagulant treatment for reasons other than VTE and follow-up of 6 patients (0.1%) was incomplete, leaving 4,421 patients available for the analysis (**Figure 1**). The 3-month VTE incidence in all patients in whom PE was excluded at baseline was 1.2% (42 events in 4421 patients; 95%CI 0.48-2.6) and the 3-month incidence of fatal PE was 0.11% (8 events in 4421 patients; 95%CI 0.02-0.70).

Table 1. Baseline characteristics for the evaluated subgroups.

Characteristic n, (%)	Total cohort n=6148	Pre-test probability category of PE	
		Unlikely n=4254	Likely n=1894
Mean age (SD)	57 (17)	56 (18)	58 (17)
Male sex	2581 (42)	1780 (42)	801 (42)
COPD	742 (12)	524 (12)	218 (12)
Heart failure	447 (7.3)	313 (7.4)	134 (7.1)
Estrogen use	576 (9.4)	424 (10)	152 (8.0)
Inpatient	804 (13)	393 (9.2)	411 (22)
Duration of complaints ≥7 days	1523 (25)	1026 (25)	461 (24)
Wells items			
Clinical signs of DVT	262 (4.3)	28 (0.7)	234 (12)
Alternative diagnosis less likely than PE	3342 (54)	1556 (37)	1786 (94)
Heart rate >100 bpm	1472 (24)	615 (14)	857 (45)
Surgery or immobilization <4 weeks	1158 (19)	381 (9.0)	777 (41)
History of VTE	993 (16)	387 (9.1)	606 (32)
Hemoptysis	301 (4.9)	187 (4.4)	114 (6.0)
Active cancer	885 (14)	462 (11)	423 (22)
PE at baseline	1307 (21)	551 (13)	756 (40)

Note: PE: pulmonary embolism; SD standard deviation; COPD: chronic obstructive pulmonary disease; DVT: deep vein thrombosis; bpm: beats per minute; n: number, VTE: venous thromboembolism.

Figure 1. Flowchart patient selection.



Note: PE: pulmonary embolism; CDR: clinical decision rule; CTPA: computed tomography pulmonary angiography.

Incidence of VTE and fatal PE in the different management categories

A total of 4,254 patients (69%) had an unlikely clinical probability and 1,894 patients (31%) a likely clinical probability. The baseline PE prevalences in these groups were 13% and 40% (**Table 1**), respectively. Of the 4,254 patients with an unlikely clinical probability, 1,586 patients (37%) had a D-dimer concentration ≤500 µg/L and could be managed without CTPA. In patients managed without CTPA, the 3-month VTE incidence was 0.71% (7 events in 1583 patients; 95%CI 0.40-1.3) and no fatal PE occurred in these patients (**Table 2**). In the remaining 2,668 patients with an unlikely clinical probability but an increased D-dimer and a normal CTPA, the 3-month incidence of VTE was 0.85% (14 events in 1792 patients; 95%CI 0.36-2.0) and of fatal PE 0.12% (3 events in 1792 patients; 95%CI 0.01-1.4).

The 3-month VTE incidence after a normal CTPA in patients with a likely clinical probability varied from 0.5% to 5.8% across the individual studies, for an overall 3-month VTE incidence of 2.0% (21 events in 1046 patients; 95%CI 1.0-4.1; **Figure 2A**), and a 3-month incidence of fatal PE of 0.48% (5 events in 1046 patients; 95%CI 0.20-1.1; **Figure 2B**). Of the 21 patients with VTE during follow-up, 9 had active cancer (47%) while only 241 of the 1,024 (24%) without VTE during follow-up had active cancer (OR 2.6; 95%CI 1.1-6.3). Also, patients with VTE during follow-up more frequently had had signs and symptoms of DVT at initial presentation: 5 of the 21 patients with VTE during follow-up (24%) versus 81 of the 1,025 patients without VTE during follow-up (7.9%) (OR 4.1; 95%CI 1.4-12) (**Table 3**). Three of the 5 patients with clinical signs of DVT at baseline and VTE during follow-up underwent compression ultrasonography of the lower extremities at baseline, of which 2 were negative for DVT and 1 demonstrated DVT. The latter patient was adju-

Table 2. The 3-month risk of VTE (A) and fatal PE (B) after PE was ruled out at baseline.

A: The 3-month risk of VTE

Diagnostic criterion	3-month risk of VTE %, (95%CI)	
Clinical probability	**Unlikely**	**Likely**
Wells score	**≤4**	**>4**
Normal D-dimer (Threshold ≤500 µg/L)	0.71 (0.40-1.3)	-
Normal CTPA	0.85 (0.36-2.0)	2.0% (1.0-4.1)

B: The 3-month risk of fatal PE

Diagnostic criterion	3-month risk of fatal PE %, (95%CI)	
Clinical probability	**Unlikely**	**Likely**
Wells score	**≤4**	**>4**
Normal D-dimer (Threshold ≤500 µg/L)	NA[1]	-
Normal CTPA	0.12% (0.01-1.4)	0.48% (0.20-1.1)

Note: PE: pulmonary embolism; CTPA: computed tomography pulmonary embolism; [1]not estimatable due to zero events.

dicated as a failure of the algorithm. Of two other patients with clinical signs of DVT at baseline information on whether CUS had been performed could not be retrieved.

Of the 21 patients with VTE during follow-up, 13 patients were diagnosed with PE (±DVT) and 8 patients with DVT. Regarding the time between initial presentation and VTE during follow-up, 9 (4 with PE, 5 with DVT) were diagnosed within 1 month after presentation, 6 (4 with PE and 2 with DVT) were diagnosed between 1 and 2 months after presentation and 6 (5 with PE and 1 with DVT) were diagnosed more than 2 months after presentation. Of the 12 patients with VTE more than 1 month after initial presentation, 8 patients (67%) had active cancer and 9 were diagnosed with PE (±DVT).

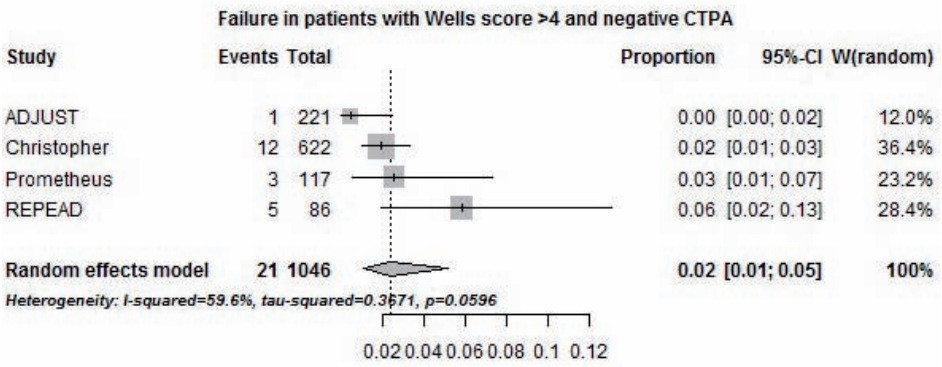
The 3-level diagnostic algorithm

When the 3-level diagnostic algorithm would have been applied, 2,314 patients (38%) would have been categorized in the low clinical probability category, 3,538 patients (58%) in the moderate clinical probability and 296 patients (4.8%) in the high clinical probability category, with PE baseline prevalences of 7.9%, 27% and 56% respectively. Baseline characteristics for the different subgroups are available in Appendix C (https://th.schattauer.de).

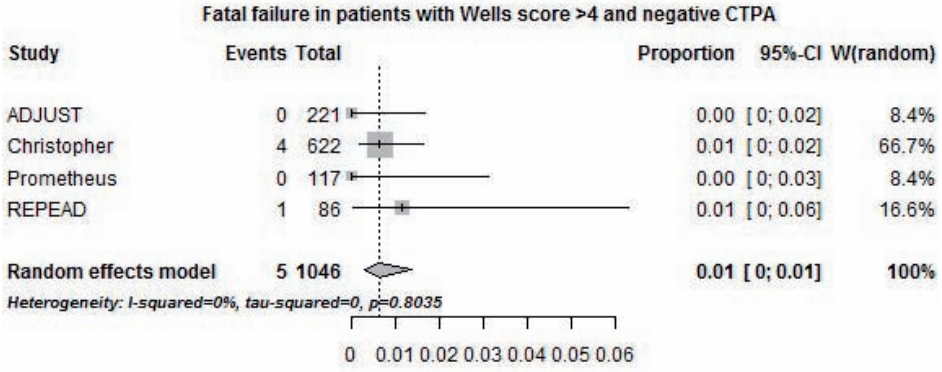
The 3-month VTE risk in patients managed without CTPA based on a low clinical probability and a D-dimer test ≤500 µg/L was 0.44% (3 events in 965 patients; 95%CI 0.17-1.2) and no fatal PE occurred among these patients. In patients with a low clinical probability and a D-dimer concentration >500 µg/L the 3-month VTE risk was 0.54% (5 events in 920 patients; 95%CI 0.23-1.3) and the 3-month risk of fatal PE was 0.11% (1 events in 920 patients; 95%CI 0.02-0.76) after a negative CTPA. In patients with an intermediate clinical probability, the 3-month VTE risk was 2.8% (18 events in 784 patients; 95%CI 1.7-4.7) after a D-dimer concentration ≤500 µg/L and 1.2% (21 events in 1645 patients; 95%CI 0.26-5.2) after a D-dimer concentration >500 µg/L and a negative CTPA. The corresponding 3-month risks of fatal PE were 0.29% (1 events in 784 patients; 95%CI

Figure 2. The 3-month risk of (A) VTE and fatal PE (B) after a normal CTPA in patients with a likely clinical probability.

A: The 3-month risk of VTE



B: The 3-month risk of fatal PE



Note: VTE: venous thromboembolism; PE: pulmonary embolism; CTPA: computed tomography pulmonary angiography.

0.07-1.1) and 0.29% (5 events in 1645 patients; 95%CI 0.09-0.92) respectively. In patients with a high clinical probability, the 3-month VTE risk after negative CTPA was 6.3% (7 events in 111 patients; 95%CI 3.0-12.6) and a 3-month risk of fatal PE was 0.90% (1 event in 111 patients; 95%CI 0.13-6.1).

DISCUSSION

The key findings of our study are the 3-month incidence of VTE of 2.0% and the risk of fatal PE of 0.48% after a normal CTPA as single imaging test in patients with a likely clinical probability of PE according to the Wells rule. In order to determine whether these

Table 3. Characteristics of patients with a likely clinical probability in whom PE was ruled out and had VTE during follow-up.

Baseline characteristics n, (%)	Patients in whom PE was excluded and no PE during follow-up n=1025	Patients who developed VTE during 3-month follow-up after a negative CTPA n=21	Odds ratio (95%CI)
Mean age (SD)	58 (17)	57 (17)	N.A.
Male sex	397 (39)	5 (24)	0.49 (0.18-1.4)
COPD	147 (14)	2 (9.5)	0.64 (0.15-2.8)
Heart failure	81 (7.9)	2 (9.5)	1.3 (0.3-5.9)
Estrogen use	67 (6.5)	3 (14)	2.7 (0.77-9.7)
Inpatient	229 (22)	5 (24)	1.1 (0.39-3.0)
Duration of complaints ≥7 days	237 (23)	4 (19)	0.80 (0.26-2.4)
Wells items			
Clinical signs of DVT	81 (7.9)	5 (24)	**4.1 (1.4-12)**
Alternative diagnosis less likely than PE	968 (94)	19 (90)	0.43 (0.10-1.9)
Heart rate >100 bpm	474 (46)	9 (43)	0.92 (0.38-2.2)
Surgery or immobilization <4 weeks	419 (41)	11 (52)	1.9 (0.76-4.8)
History of VTE	297 (29)	8 (38)	1.5 (0.62-3.7)
Hemoptysis	55 (5.4)	1 (4.8)	0.95 (0.13-7.3)
Active cancer	241 (24)	9 (43)	**2.6 (1.1-6.3)**

Note: PE: pulmonary embolism; VTE: venous thromboembolism; CI: confidence interval; n: number of patients; CTPA: computed tomography pulmonary angiography; SD: standard deviation; COPD: chronic obstructive pulmonary disease; DVT: deep vein thrombosis; bpm: beats per minute; N.A: not applicable.

results support ruling out PE by a normal CTPA alone, several considerations should be taken into account.

First and most importantly, the incidence of VTE of 2.0% as well as the incidence of fatal PE of 0.48% after a normal CTPA in patients with a likely clinical probability identified in our study compare well to the same incidences after a normal pulmonary angiography - 1.7% (95%CI 1.0-2.7) for VTE and 0.3% (95%CI 0.02-0.7) for fatal PE - which is the gold standard in PE diagnosis [20].

Second, although our results demonstrate that the VTE incidence after a negative CTPA is higher in patients with a likely clinical probability compared to the incidences observed in patients with an unlikely clinical probability, this has to be interpreted as an inevitable consequence of Bayes' theorem. Since the sensitivity of CTPA - as for all other relevant available diagnostic tests for PE - is known to be slightly less than 100%, a higher clinical probability results in a slight decrease of the negative predictive value. Therefore and in general, the overall PE prevalence in study population should always be taken into account when interpreting the VTE incidence after PE had been ruled out.

In our study, the PE prevalence in patients with a likely clinical probability was 40%. In the studies included in the meta-analysis of van Beek and colleagues in which the safety of a normal pulmonary angiography was investigated, the PE prevalence varied from 20% to 33% [20]. Consequently, it can be reasonably expected that the VTE incidence after a normal pulmonary angiogram in our patients with a likely clinical probability, in whom the PE prevalence of 40% was notably higher, would have exceeded the 1.7% reported in this meta-analysis. Moreover, a recent SSC recommendation suggested using a diagnostic safety threshold in PE studies that is dependent on the disease prevalence at baseline [21]. According to the suggested formula, the safety threshold for studies with a baseline PE prevalence of 40% is 2.0%, which is in line with our findings.

We acknowledge that when focussing on the small subgroup of patients with a high clinical probability according to the Wells rule (less than 5% of total study population), the 3-month VTE incidence is non negligible. Importantly, there is no diagnostic test after CTPA available that has been shown to improve the patient's prognosis, except for CUS in patients who also have symptoms of DVT [4]. Our results thus demonstrate that clinicians should be alert on the occurrence of VTE at follow-up after a normal CTPA in these latter patients.

In our view, an individualized patient management is much preferred over performing additional diagnostic tests in all patients, since it is highly unlikely that such a strategy will lead to an acceptable yield, when performed in all patients.

Active cancer and signs of DVT were shown to be predictive of developing VTE during follow-up. The first patient category has an intrinsic very high risk of VTE, with an overall OR varying from 4.1 to 6.7 compared to patients without cancer resulting in an annual risk varying from 0.5 to 20% [22-24]. Consequently, the question arises whether VTE in cancer patients after a normal CTPA could be newly formed VTE rather than initially missed VTE. With regard to the latter category, at least 3 of the 5 patients with a negative CTPA but clinical signs of DVT and a VTE during follow-up were subjected to CUS at baseline. A negative CUS did not prevent the occurrence of VTE, which supports previous studies, indicating that baseline CUS after negative CTPA in patients without signs of DVT does not further diminish the VTE incidence during follow-up [4, 12-14]. Of note, a positive baseline CUS may be regarded as a somewhat doubtful criterion for failure of the PE algorithm since the algorithm aims to rule out PE and not symptomatic DVT. Moreover, CT venography might be considered as an additional test after a normal CTPA, since the PIOPED 2 study demonstrated an improvement of the sensitivity by adding this test to a 4 to 16-row CTPA [25]. However, it should be emphasized that the PIOPED 2 study was a diagnostic accuracy study. In a clinical outcome study the key question is the incidence of recurrent VTE during follow-up in those patients with initially normal diagnostic tests. By design, this question could not be answered by the PIOPED-2 study and as a result the true value of adding CT venography with respect to clinical outcome at 3 months

is still uncertain. Moreover, the CTPA technology used in the PIOPED-2 study, i.e. 4 to 16-row CTPA, has become outdated since in current clinical practice 254-row CTPA is used with resulting higher sensitivity. Therefore, future studies are required in order to determine whether our findings still reflect current daily clinical practice.

Recently, another study investigated the safety of excluding PE based on a normal CTPA alone [26]. In this observational study, 134 patients with a high clinical probability (Wells rule score >6 points) but a normal CTPA were described. Of these patients, 48 patients (36%) underwent additional testing, either CUS or ventilation/perfusion-scanning, after which 4 patients were diagnosed with DVT and 2 with PE. It should be noted that it is unclear how these patients were selected and whether these 4 patients with DVT had symptoms suggesting of DVT. Likely, this was based on their symptoms and other clinical characteristics. These patients represented a highly selected subgroup from a total cohort of 3237 patients (1.5%). Together with 2 symptomatic PE diagnoses during follow-up, the hypothetical 3-month VTE incidence after a normal CTPA would have been 5.2% (7/134; 95%CI 1.5-9.0). These results are quite in line with our findings and underline our suggested strategy of a stricter follow-up of patients with a high clinical probability but a normal CTPA and considering additional testing only in selected patients.

Strengths of our study are the large number of included patients, the availability of patient-level data from 4 large prospective studies and the highly comparable study designs of all included studies. Additionally, it should be noted that in three of the included studies single row and 4-row CTPA were used, of which the sensitivity is known to be relatively low compared to nowadays multi-row CTPA [1, 2, 15]. Therefore, the safety of a normal CTPA reported in this study may even be an underestimation of the safety of the multi-row CTPA machines currently used in clinical practice, further supporting our conclusion. The major limitation of our study is the fact that we only evaluated 4 studies and did not perform a full systematic review and meta-analysis of all available literature, but rather used data from 4 homogeneous studies. Also, differences in the CT imaging quality between the individual studies were present among the individual studies and we could not retrieve information on CUS examinations of 2 of the 5 patients with a likely probability of PE and symptoms suggestive of DVT at baseline, who were diagnosed with VTE during follow-up after a normal CTPA. Nonetheless, we do not dispute the clear indication for CUS in those particular patients. Last, the post-hoc analysis of the group of patients with an intermediate clinical probability (Wells score 2-6 points) may have introduced differential verification bias since patients with a Wells score of 4.5-6 points underwent CTPA regardless of their D-dimer result. Consequently, we may have overestimated the failure rate in patients with an intermediate probability and a negative D-dimer due to false-positive CTPA results and PE that would have resolved without anticoagulant treatment otherwise.

In conclusion, our study suggests that the risk of VTE and fatal PE after a normal CTPA in patients with a likely clinical probability is comparable to these risks after a normal pulmonary angiogram. Therefore, a normal CTPA alone may be considered as a valid diagnostic criterion to rule out PE in the majority of patients with a likely clinical probability of PE assessed by the Wells rule. Nevertheless, the risk of fatal PE after a normal CTPA alone is relatively high, particularly in patients with concomitant signs of DVT, active cancer and those with a Wells rule >6 points. Consequently, clinicians should consider a closer follow-up in selected patients preferably with a personalised approach. Further studies are required to determine whether the modern multi-row CTPA result in a higher accuracy than the 4 to 64-row CTPA used in the included studies.

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CHAPTER 5

Variable D-dimer thresholds for diagnosis of clinically suspected acute pulmonary embolism

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ABSTRACT

Background

Computed tomography pulmonary angiography (CTPA) is frequently requested using diagnostic algorithms for suspected pulmonary embolism (PE). For suspected deep vein thrombosis, it was recently shown that doubling the D-dimer threshold in patients with low pretest probability safely decreased the number of ultrasonograms. We evaluated the safety and efficiency of a similar strategy in patients with suspected PE.

Methods

We performed a post-hoc analysis of 2213 consecutive patients of two cohort studies with suspected PE who were managed according to current standards: PE ruled out in case of unlikely probability (Wells rule ≤ 4 points) and a D-dimer level < 0.5 µg/mL. CTPA was performed in all other cases. All patients were followed for 3 months. We calculated 3-month venous thromboembolism (VTE) incidence and the number of required CTPAs for selective D-dimer thresholds in patients with low clinical probability (< 2 points, D-dimer threshold < 1.0 µg/mL) and intermediate probability (2–6 points, D-dimer threshold < 0.5 µg/mL).

Results

Using standard management, PE could be excluded without CTPA in 26% of patients, with a 3-month VTE incidence of 0.88% (95% confidence interval [CI] 0.29–2.1%). Using selective D-dimer thresholds, PE could be excluded without CTPA in 36% of patients, with a 3-month VTE incidence of 2.1% (95% CI 1.2–3.4%) in patients managed without CTPA, an increase of 1.2 percentage points (95% CI −0.3 to 2.2).

Conclusions

Applying selective D-dimer thresholds reduces the need for CTPA by 11 percentage points but is associated with an increased failure rate. Prospective studies should evaluate the safety and net clinical benefit of this approach.

INTRODUCTION

The preferred diagnostic algorithm for patients with suspected acute pulmonary embolism (PE) combines sequential testing with a clinical decision rule (CDR), categorizing patients into either unlikely or likely pretest clinical probability, followed by D-dimer testing and computed tomography pulmonary angiography (CTPA). This algorithm has been demonstrated to be safe and efficient with a 3-month venous thromboembolism (VTE) incidence < 2% [1]. Importantly, this diagnostic strategy obviates the need for CTPA in 20–30% of all referred patients and allows a fast and effective management decision in 98% of cases [1, 2]. Nonetheless, the low specificity of both D-dimer tests and CDR leads to a high frequency of false-positive results, in turn leading to a high number of 70–80% negative CTPAs [2, 3]. Since CTPA is associated with long-term radiation complications, allergic reactions to iodinated contrast material, contrast-induced nephropathy, and higher health care costs, one of the major challenges in the diagnostic workup of patients with suspected PE is to safely diminish the number of CT scans [4-6].

Several attempts have been made to accomplish a higher specificity of the D-dimer test for the diagnosis of acute PE. Previous studies that attempted to improve D-dimer specificity by increment of the D-dimer or CDR score cutoff levels led to increases in 3-month VTE incidence [7, 8]. For example, increasing the threshold of the CDR from 4 to 5 points resulted in a 3-month VTE incidence of 1.5% (95% confidence interval [CI] 0.6–3.0%) instead of 0.9% (95% CI 0.3–2.4%) and only increasing the D-dimer threshold from ≤ 0.5 μg/mL to ≤ 0.6 μg/mL resulted in a 3-month VTE incidence of 2.2% (95 CI 1.1–4.0%) [8]. The introduction of an age-dependent D-dimer threshold from < 0.5 μg/mL to patient's age × 10 ng/mL (for patients aged > 50) led to a decrease in the number of performed CT scans of 6 percentage points in a post-hoc analysis with 3-month VTE incidence of 0.2% (95% CI 0–1.0%) [9]. The safety of this strategy is currently being evaluated prospectively. However, no previous study investigated variable D-dimer thresholds dependent on pretest probability in PE-suspected patients.

A recent study reintroduced the three pretest probability categories, instead of two categories, of the Wells decision rule in patients with suspected deep venous thrombosis (DVT) to evaluate whether a higher D-dimer cutoff level (< 1.0 μg/mL instead of < 0.5 μg/mL) is safe in the lowest pretest probability category [10]. This strategy reduced the proportion of required ultrasonography by 7.6 percentage points without a decrease in the negative predictive value (NPV). This would be of particular interest for patients with suspected PE, since it has been estimated that nearly one-third of all CTPAs are performed in patients with a D-dimer level < 1.0 μg/mL [11].

Therefore, we evaluated the safety and efficiency of a comparable strategy, an algorithm with three different pretest probability categories and an increased D-dimer threshold of 1.0 μg/mL in patients with a low pretest probability. We will compare the

3-month VTE incidence rate and the required number of CTPAs of this strategy to the current standard algorithm with a two-level Wells rule outcome and a fixed 0.5 µg/mL D-dimer threshold for patients with a 'PE unlikely' risk score.

METHODS

Patients

Data were obtained from two previously published multicenter prospective management studies performed in the Netherlands in patients with suspected PE [2, 3]. Both inpatients and outpatients with suspected PE were included. Exclusion criteria were treatment with therapeutic doses of unfractionated or low-molecular-weight heparin for > 24 hours, treatment with vitamin K antagonists, life expectancy < 3 months, pregnancy, geographic inaccessibility precluding follow-up, age < 18 years, allergy to intravenous contrast agents, renal insufficiency (creatinine clearance < 30 mL/min), logistic reasons (e.g. unavailability of CT, patient too ill to undergo CT scanning), and hemodynamic instability. In the Prometheus study, previous PE also was an exclusion criterion. In all patients, the Wells rule was calculated [12]. The Christopher Study was a prospective cohort study conducted from November 2002 through December 2004 to evaluate a diagnostic algorithm consisting of sequential application of a clinical decision rule, D-dimer testing, and a CT scan within 24 hours of presentation [2]. According to the study protocol, D-dimer tests were performed only in case of an unlikely clinical probability assessed with use of the Wells rule. Even so, in 5 of 12 participating hospitals, D-dimer levels were also measured post-hoc in patients with a likely clinical probability for scientific purposes. Only patients from these hospitals (1614 of a total of 3306 patients) were included in the present analysis. The Prometheus study, conducted from July 2008 through November 2009, aimed to compare four clinical decision rules for suspected acute PE, including the Wells rule, using a computerized scoring system [3]. By protocol, D-dimer levels were assessed in all patients. In both studies, PE was ruled out in patients with an unlikely clinical probability in combination with a normal D-dimer test. In case of either a likely clinical probability or an elevated D-dimer level, patients were referred for CTPA and managed according to the CTPA result. All patients provided informed consent, and both studies were approved by the institutional review boards of all participating hospitals. Among the study centers, different high-sensitivity D-dimer assays were used: VIDAS D-Dimer Assay (bioMérieux, Marcy-l'Étoile, France), Tina-Quant Assay (Roche Diagnostica, Mannheim, Germany), STA Liatest D-Di (Diagnostica Stago, Asnières-sur-Seine, France), or Innovance D-Dimer (Siemens, Marburg, Germany).

Outcome and follow-up

All patients were followed for 3 months to evaluate the occurrence of symptomatic VTE (i.e. PE and/or DVT). An independent adjudication committee evaluated all episodes of suspected VTE and deaths. Deaths were classified as caused by PE in case of confirmation by autopsy, in case of an objective test positive for PE before death, or if PE could not be confidentially excluded as the cause of death. In case of clinically suspected VTE, an objective clinical test was performed (i.e. compression ultrasound for suspected DVT and a ventilation-perfusion scintigraphy or CTPA for suspected PE). Primary outcomes of the current analysis were the objective diagnosis of symptomatic DVT or PE in the 3-month period following study inclusion.

Standard diagnostic algorithm

Patients with a Wells score ≤ 4 points were categorized as 'PE unlikely', and patients with a Wells score > 4 points as 'PE likely'. In patients with a 'PE unlikely' score, a D-dimer test was indicated. In patients with a D-dimer level < 0.5 µg/mL, a PE was excluded without further testing. In patients with a D-dimer level ≥ 0.5 µg/mL or a 'PE likely' risk score, CTPA was indicated [1, 2].

Study algorithm

Patients with a Wells score < 2 points were categorized as low risk, patients with a Wells score of 2–6 points as moderate risk, and patients with a Wells score > 6 points as high risk. In patients with a lowrisk score, we evaluated an increased D-dimer threshold of < 1.0 µg/mL, while the D-dimer threshold in patients with a moderaterisk score remained at < 0.5 µg/mL. In patients with a D-dimer level equal to or above the specific threshold and in patients with a highrisk score, CTPA was indicated. In addition, we evaluated D-dimer thresholds between 0.5 µg/mL and 1.0 µg/mL with increments of 0.1 µg/mL in patients with a lowrisk category, while the threshold in patients with a moderaterisk score remained at < 0.5 µg/mL. Finally, we performed the analysis for hospitalized patients and outpatients separately.

Statistics

For each predefined pretest probability/D-dimer threshold scenario, the diagnostic failure rates, defined as the 3-month VTE incidence, were calculated in patients managed without CTPA and in all patients in whom a PE was excluded at baseline (including occurrences after a negative CTPA), with exact binomial 95% CIs. The difference of the 3-month VTE incidence between the standard algorithm and the study algorithm were assessed with use of 95% CIs. The number of CTPAs performed was calculated. The sensitivity, specificity, NPV, and positive predictive value (PPV) for both algorithms were calculated. For this calculation, we defined a positive test result as either a 'PE likely' or

high-risk Wells score or a D-dimer level equal to or above the specific D-dimer threshold. A diagnosis of PE was defined as either PE at baseline or DVT or PE during 3-month follow-up.

RESULTS

Of 2421 eligible patients, 159 were excluded because of missing D-dimer results, 3 because individual items of the Wells score were missing, and 46 because of treatment with anticoagulants for reasons other than VTE during follow-up, leaving a total of 2213 patients available for the current analysis (**Table 1**). Mean age was 53 years, and 57% of patients were female. The overall prevalence of PE was 23% (488 patients diagnosed with PE at baseline and 13 in the 3-month follow-up period). The mortality attributable to PE was 1.0% (5 of 488, 95% CI 0.3–2.4%) in patients diagnosed with PE at baseline and 15.4% (2 of 13, 95% CI 1.9–45.5%) in those who were diagnosed with PE during the follow-up period after a PE was excluded at baseline. Of these two patients, one had a CDR risk score of 4.5 points and a D-dimer level of 2400 µg/mL and the other patient had a CDR risk score of 5.5 points and a D-dimer level of 449 µg/mL. Based on these results, both patients were subjected to CTPA using the standard algorithm, with a false-

Table 1. Baseline characteristics of the study population (n = 2213).

Characteristics						
	Total population (n=2213)	**Dichotomised CDR outcome**		**Original three pre-test probability categories**		
		Unlikely (n=1517)	**Likely (n=696)**	**Low (n=755)**	**Moderate (n=1347)**	**High (n=111)**
Age in years	53 (SD 18)	52 (SD 18)	56 (SD 18)	51 (SD 18)	54 (SD 18)	58 (SD 16)
Female sex (n, %)	1259 (57%)	868 (57%)	391 (56%)	444 (59%)	750 (56%)	65 (59%)
Estrogen use (n, % of females)	260 (21%)	194 (22%)	66 (17%)	94 (21%)	155 (21%)	11 (17%)
Immobilization > 3 days or surgery (n, %)	480 (22%)	140 (9.2%)	340 (49%)	72 (9.5%)	331 (25%)	77 (69%)
History of VTE (n, %)	232 (10%)	90 (5.9%)	142 (20%)	62 (8.2%)	139 (10%)	31 (28%)
COPD (n, %)	220 (9.9%)	152 (10%)	68 (10%)	78 (10%)	133 (9.9%)	9 (8.1%)
Heart failure (n, %)	167 (7.5%)	115 (7.6%)	52 (7.5%)	61 (8.1%)	98 (7.3%)	8 (7.2%)
Malignancy (n, %)	375 (17%)	212 (14%)	163 (23%)	76 (10%)	247 (18%)	52 (47%)
Outpatients (n, %)	1729 (78%)	1267 (84%)	462 (66%)	646 (86%)	1013 (75%)	70 (63%)
PE at baseline (n, %)	488 (22%)	216 (14%)	272 (39%)	53 (7.0%)	371 (28%)	64 (58%)
Median D-dimer result (IQR) (µg/mL)	1.0 (0.40-2.3)	0.70 (0.30-1.7)	1.8 (0.81-4.0)	0.56 (0.28-1.2)	1.2 (0.51-2.7)	3.1 (1.3-5.7)

Note: CDR: clinical decision rule; SD: standard deviation; VTE: venous thromboembolism; COPD: chronic obstructive pulmonary disease; PE: pulmonary embolism; IQR: interquartile range.

negative result. However, when the study algorithm would have been applied, this CTPA would have been withheld in the latter patient. **Table 1** additionally depicts the baseline characteristics for all different risk categories by the Wells rule. VTE risk factors, including previous VTE, recent immobilization or surgery, and malignancy, were more prevalent in categories with a higher pretest probability. The median D-dimer levels were higher in patients with a higher pretest probability. Table S1 (available at http://onlinelibrary.wiley.com/journal/10.1111/(ISSN)1538-7836/) provides baseline characteristics of the patients included in the original studies.

With use of the dichotomized algorithm, 69% (1517 of 2213) of patients had a 'PE unlikely' pretest probability and 31% (696 of 2213) had a 'PE likely' pretest probability, with a PE incidence at baseline of 14% and 39%, respectively. When applying the original three-level CDR risk score, 34% (755 of 2213) were categorized as low, 61% (1347 of 2213) as moderate, and 5% (111 of 2213) as high clinical probability. The PE incidences at baseline in these categories were 7.0%, 28%, and 58%, respectively.

In the standard algorithm, using the dichotomized Wells rule combined with a D-dimer threshold of < 0.5 µg/mL, additional testing with CTPA was needed in 74.4% (1646 of 2213) of the patients, of whom 30% showed PE. The 3-month VTE incidence in patients in whom PE was excluded with CDR and D-dimer was 0.88% (5 of 567, 95% CI 0.29–2.1%), and it was 0.93% (16 of 1717, 95% CI 0.53–1.5%) in all patients in whom a PE was excluded at baseline (**Table 2**). The sensitivity of the algorithm was 99.0% (95% CI 97.7–99.7%), with a specificity of 32.8% (95% CI 30.6–35.1%), NPV of 99.1% (95% CI 98.0–99.7%), and PPV of 30.1% (95% CI 27.9–32.4%), and the area under the receiver operating characteristic (ROC) curve was 0.66 (95% CI 0.64–0.68). Of the five patients with a false-negative algorithm result, four patients had a PE (three had peripherally

Table 2. Influence of varying D-dimer cut-offs in different CDR risk categories.

Number of CDR-risk groups	D-dimer cut-off level in unlikely risk category (µg/mL)	D-dimer cut-off level in low risk category (µg/mL)	D-dimer cut-off level in moderate risk category (µg/mL)	3-month VTE recurrence rate			Percentage CTPA performed in total population	Percentage CTPA positive for PE
				In patients managed without CTPA		In patients without a diagnosis of PE at baseline		
				n	% (95% CI)	% (95% CI)		
2	<0.5	-	-	5	0.88 (0.29-2.1)	0.93 (0.53-1.5)	74.4%	30%
3	-	<0.5	<0.5	10	1.5 (0.74-2.8)	1.2 (0.71-1.8)	70.8%	31%
3	-	<1.0	<0.5	17	2.1 (1.2-3.4)	1.5 (1.0-2.3)	63.7%	34%

Note: CDR: clinical decision rule; VTE: venous thromboembolism; CTPA: computed tomography pulmonary angiography.

located PE, in one patient the exact location was not specified) and one patient had a DVT. None of these patients died during follow-up.

Using the three Wells categories in combination with a D-dimer threshold in the low-risk and the moderate-risk category of < 0.5 µg/mL, CTPA was needed in 70.8% (1566 of 2213) of the patients, of whom 31% were positive for PE. The 3-month VTE incidence in patients in whom PE was excluded based on a low CDR risk score or a moderate-risk score and D-dimer < 0.5 µg/mL was 1 of 346 and 9 of 301, respectively, resulting in a 3-month VTE recurrence rate in patients managed without CTPA of 1.5% (10 of 647, 95% CI 0.74–2.8%). The 3-month VTE recurrence rate in all patients in whom PE was excluded at baseline was 1.2% (20 of 1722, 95% CI 0.71–1.8%). The sensitivity of the algorithm was 98.0% (95% CI 96.4–99.0%), the specificity was 37.2% (95% CI 34.9–39.6%), the NPV was 98.5% (95% CI 97.2–99.3%), the PPV was 31.4% (95% CI 29.1–33.7%), and the area under the ROC curve was 0.68 (95% CI 0.65–0.70).

When raising the D-dimer cutoff level to 1.0 µg/mL, the number of needed CT scans in the total cohort decreased from 74.4% (1646 of 2213) to 63.7% (1409 of 2213) (difference with the current standard algorithm of 10.7 percentage points [95% CI 8.0–13.4]). The 3-month VTE incidence was 8 of 503 in patients with a low-risk CDR score and a negative D-dimer threshold and 9 of 301 in patients with a moderate-risk CDR score and a negative D-dimer threshold, resulting in a 3-month VTE incidence of 2.1% (17 of 804, 95% CI 1.2–3.4%). The diagnostic failure rate in all patients in whom PE was excluded at baseline was 1.5% (27 of 1729, 95% CI 1.0–2.3%). The differences with the standard algorithm were 1.2 percentage points (95% CI −0.3 to 2.2) in patients managed without CTPA and 0.57 percentage point (95% CI −0.2 to 1.3) in all patients in whom a PE was excluded at baseline (thus including patients with a CTPA negative for PE at baseline). Also, this scenario resulted in an increase of the specificity to 46.0% (95% CI 43.6–48.4%) and a decrease of the NPV to 97.9% (95% CI 96.6–98.8%). The sensitivity was 96.6% (95% CI 94.9–98.0%), the PPV was 34.4% (95% CI 31.9–36.9%), and the area under the ROC curve was 0.71 (95% CI 0.69–0.74). Of the additional 11 patients in whom PE was falsely excluded by applying the study algorithm, 6 patients had a subsegmental PE, 2 had a segmental PE, 2 patients had a central PE, and in 1 patient the exact localization was not specified.

Applying fixed D-dimer thresholds levels between 0.5 and 1.0 µg/mL (with increments of 0.1 µg/mL) in the low-risk category while the D-dimer threshold remained at < 0.5 µg/mL in the moderate-risk group did not result in more favorable diagnostic failure rates (data not shown). When analyzing outpatients only with the study algorithm, the 3-month VTE incidence rate was 1.9% (95% CI 1.0–3.1%) in patients managed without CTPA and 1.3% (95% CI 0.8–2.0%) in all patients in whom PE was excluded at baseline. The number of patients who were managed without CTPA increased from 31.4% to 43.2%, an increase of 11.8 percentage points (95% CI 8.5–15.0). When we performed the

same analysis in hospitalized patients only, the 3-month VTE incidence rates were 5.3% (95% CI 1.1–14.6%) and 2.6% (95% CI 1.2–4.8%), respectively. The number of patients managed without CTPA increased from 5.0% to 11.8%, an increase of 6.8 percentage points (95% CI 3.2–9.9).

DISCUSSION

We investigated the safety of applying variable D-dimer thresholds in patients with a low clinical probability, using the three-level original pretest probability Wells score in a large cohort of patients with a clinically suspected PE, in an attempt to reduce the number of CTPA. Our study has the following interesting findings.

In patients with suspected PE, the combination of a low-risk CDR score and a D-dimer threshold of 1.0 µg/mL or an intermediate-risk CDR score with a D-dimer threshold of 0.5 µg/mL decreases the necessity of CTPA by 11 percentage points. This comes at the cost of an increase in the 3-month VTE failure rate in patients managed without CTPA of 1.2 percentage points (95% CI −0.3 to 2.2) and 0.57 percentage point (95% CI −0.2 to 1.3) in all patients in whom a PE was excluded at baseline. Also, all other D-dimer threshold modifications between 0.5 µg/mL and 1.0 µg/mL that we studied resulted in a higher 3-month VTE incidence. We were unable to define a modification of the algorithm that did not result in this increase of the 3-month VTE incidence. This contrasts with the results of the recently published study in DVT-suspected patients by applying a comparable algorithm [10]. One explanation for this difference may be the three times higher disease prevalence (23%) in our study cohort compared with the DVT cohort (7.1%); this overall DVT prevalence was lower than the PE prevalence of 7.4% in our low-risk category alone. Based on the high 3-month incidence rates of the study algorithm in hospitalized patients, we concluded that this strategy is not safe for hospitalized patients. Therefore, it seems reasonable to include outpatients only in a prospective validation study.

Traditionally, a 3-month VTE incidence of 1.7% with an upper limit of the 95% CI of 2.7% serves as the gold standard for safety in prospective diagnostic PE studies, which is the 3-month VTE incidence after a negative pulmonary angiography [13]. Although the 3-month VTE incidence in this post-hoc analysis exceeds this safety margin in patients managed without CTPA, the safety margin was not exceeded in the total cohort (all patients without PE at baseline). However, due to the design of the study, we were unable to determine the clinical outcome of the additional missed diagnoses of PE by the selective D-dimer algorithm. Therefore, these 3-month VTE incidence rates have to be interpreted cautiously. Furthermore, some observations in previous studies might suggest that subsegmental PEs may be clinically less relevant and may not require treatment [14]. First, in a diagnostic study that compared a strategy involving ventilation-

perfusion lung scanning to a CTPA-based algorithm, an additional 5.0% of patients were diagnosed with PE at baseline after CTPA compared with ventilation-perfusion lung scanning. However, the 3-month VTE incidence in patients with normal tests was not different between the strategies [15]. Second, it is known that the introduction of CTPA is associated with a rising PE incidence with only a minimal decrease in PE-related mortality, suggesting overdiagnosis [16]. The fact that the majority of the PEs that would have been missed were subsegmentally located might support this hypothesis. Therefore, only a prospective study will be able to determine the true clinical implications of the selective D-dimer strategy.

When considering the potential of applying the selective D-dimer threshold strategy in clinical practice, both its safety and feasibility should be taken into account. For that matter, the somewhat higher complexity of patients management in busy emergency departments using altered D-dimer thresholds in three probability categories compared with one general D-dimer threshold in two probability categories should be balanced against its benefit (i.e. a large saving of CTPAs, which may increase its clinical acceptation). The advantages of a diagnostic algorithm with an 11-percentage-point lower number of necessary CTPAs would be a reduction in valuable time, costs, and complications associated with performing CTPA. These complications include radiation exposure, allergic reactions to iodinated contrast material, and contrast-induced nephropathy [4-6]. The radiation dose of a single CTPA ranges from 3 to 5 mSv, with an estimated risk of 150 excess cancer deaths per 1 million exposures to a single CTPA [17]. The incidence of contrast-induced nephropathy ranges between 6.5% and 19% depending on the studied population and the definition of contrast-induced nephropathy that is used [4, 18].

Strengths of this analysis are the inclusion of two large and accurately documented cohorts from previous prospective management studies and the assessment of the primary outcome by an independent adjudication committee. The fact that our study was a post-hoc analysis is the most important study limitation. By design, we were therefore unable to establish the clinical course of the patients with a false-negative outcome of the algorithm since they received anticoagulant treatment. Another limitation is a result of the design of the original management studies, in which not all patients underwent the reference standard at baseline, CTPA. The fact that not all patients in whom PE was excluded in the study algorithm based on a low or intermediate probability combined with a negative D-dimer test result underwent the same verification test (i.e. clinical follow-up or CTPA) may have introduced verification bias. Furthermore, the exclusion of patients in whom no D-dimer test was performed is a limitation.

In conclusion, raising D-dimer thresholds in different pretest probability categories results in a decrease in the number of required CTPAs and an increase in the failure rate of the chosen algorithm. Applying the original three-level Wells rule for PE with a D-dimer cutoff level of < 1.0 µg/mL for patients with a low pretest probability for PE

and a cutoff level of < 0.5 µg/mL for patients with an intermediate pretest probability for PE resulted in a 3-month VTE incidence of 2.1% in patients managed without CTPA and 1.5% in whom a PE was excluded at baseline. However, since the outcome of the undiagnosed PE patients is unknown in this post-hoc analysis, a prospective study is needed to evaluate the safety and net clinical benefit of this approach. Also, a formal cost-effectiveness analysis will aid in conclusively establishing whether changing the current standard diagnostic strategy will result in a more optimal diagnostic management of suspected PE.

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CHAPTER 6

Simplified diagnostic management of suspected pulmonary embolism (the YEARS study): a prospective, multicentre, cohort study

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ABSTRACT

Background

Validated diagnostic algorithms in patients with suspected pulmonary embolism are often not used correctly or only benefit subgroups of patients, leading to overuse of computed tomography pulmonary angiography (CTPA). The YEARS clinical decision rule that incorporates differential D-dimer cutoff values at presentation, has been developed to be fast, to be compatible with clinical practice, and to reduce the number of CTPA investigations in all age groups. We aimed to prospectively evaluate this novel and simplified diagnostic algorithm for suspected acute pulmonary embolism.

Methods

We did a prospective, multicentre, cohort study in 12 hospitals in the Netherlands, including consecutive patients with suspected pulmonary embolism between Oct 5, 2013, and July 9, 2015. Patients were managed by simultaneous assessment of the YEARS clinical decision rule, consisting of three items (clinical signs of deep vein thrombosis, haemoptysis, and whether pulmonary embolism is the most likely diagnosis), and D-dimer concentrations. In patients without YEARS items and D-dimer less than 1000 ng/mL, or in patients with one or more YEARS items and D-dimer less than 500 ng/mL, pulmonary embolism was considered excluded. All other patients had CTPA. The primary outcome was the number of independently adjudicated events of venous thromboembolism during 3 months of follow-up after pulmonary embolism was excluded, and the secondary outcome was the number of required CTPA compared with the Wells' diagnostic algorithm. For the primary outcome regarding the safety of the diagnostic strategy, we used a per-protocol approach. For the secondary outcome regarding the efficiency of the diagnostic strategy, we used an intention-to-diagnose approach. This trial is registered with the Netherlands Trial Registry, number NTR4193.

Findings

3616 consecutive patients with clinically suspected pulmonary embolism were screened, of whom 151 (4%) were excluded. The remaining 3465 patients were assessed of whom 456 (13%) were diagnosed with pulmonary embolism at baseline. Of the 2946 patients (85%) in whom pulmonary embolism was ruled out at baseline and remained untreated, 18 patients were diagnosed with symptomatic venous thromboembolism during 3-month follow-up (0.61%, 95% CI 0.36–0.96) of whom six had fatal pulmonary embolism (0.20%, 0.07–0.44). CTPA was not indicated in 1651 (48%) patients with the YEARS algorithm compared with 1174 (34%) patients, if Wells' rule and fixed D-dimer threshold of less than 500 ng/mL would have been applied, a difference of 14% (95% CI 12–16).

Interpretation

In our study pulmonary embolism was safely excluded by the YEARS diagnostic algorithm in patients with suspected pulmonary embolism. The main advantage of the YEARS algorithm in our patients is the absolute 14% decrease of CTPA examinations in all ages and across several relevant subgroups.

INTRODUCTION

The clinical diagnosis of pulmonary embolism is non-specific and should therefore be followed by objective testing. Because of its diagnostic accuracy and wide availability, multidetector row computed tomography pulmonary angiography (CTPA) is the imaging test of choice to confirm acute pulmonary embolism in most patients. Increasing use of CTPA with diminishing prevalence of pulmonary embolism —to even less than 10% [1]— has led to overdiagnosis of mostly subsegmental pulmonary embolism and unnecessary risks of radiation exposure and contrast medium induced nephropathy [2–6]. To avoid these problems, validated diagnostic algorithms for suspected acute pulmonary embolism, using sequential testing, have been introduced [7]. In these algorithms, a normal D-dimer test result in patients with low probability safely excludes pulmonary embolism [8]. Correct application of these algorithms obviates the need for CTPA in 20–30% of patients, with an overall 3-month diagnostic failure rate of less than 1.5% after initial negative ruling of the algorithm [7–9]. An age-adjusted D-dimer threshold (age × 10 ng/mL for patients aged >50 years) has been validated prospectively, reporting an absolute reduction of 11.6% (95%CI 10.5–12.9) in the need for CTPA [10]. Importantly, only patients aged 50 years or older, and foremost those older than 75 years benefit from this strategy whereas when considering the life-time attributable cancer risk, the exposure to unnecessary radiation is considered more relevant to younger individuals, particularly women [3].

Despite firm evidence of its safety and efficiency, adherence to recommended diagnostic strategies in clinical practice is variable. This variation might be partly due to complexity of these strategies, and insufficient time at busy emergency departments, which hampers the use of sequential tests [11–14]. In daily practice, D-dimer testing is frequently ordered and known at low clinical threshold or even before the clinical assessment [15,16]. Improved adherence to the algorithm, for instance by implementation of a clinical decision support system, has been shown to significantly decrease the mean number of diagnostic tests used along with —and more importantly— the number of diagnostic failures [17,18].

On the basis of a post-hoc derivation and validation study [19], three items of the original Wells' clinical decision rule —ie, clinical signs of deep vein thrombosis, haemoptysis, and whether pulmonary embolism is the most likely diagnosis— were the most predictive for pulmonary embolism. They allowed the use of a differential D-dimer threshold based on the presence of one of these items, without losing sensitivity. Hence, this algorithm —which we call YEARS— involves the simultaneous assessment of only the three abovementioned items and a D-dimer test threshold of 500 ng/mL in presence, and 1000 ng/mL in absence of one of the YEARS items. The YEARS algorithm was designed to be more easily applied in a busy clinical practice than currently used diag-

nostic strategies, and to further decrease the number of necessary CTPA examinations in patients of all ages. In this study, we aimed to prospectively evaluate this novel and simplified diagnostic algorithm for suspected acute pulmonary embolism.

METHODS

Study design and patients

We did a prospective, multicentre, cohort outcome study evaluating the safety and efficiency of the YEARS algorithm in patients with suspected acute pulmonary embolism between Oct 5, 2013, and July 9, 2015 **(Figure 1)** [19]. The algorithm was implemented as standard diagnostic strategy in 12 participating hospitals in the Netherlands. The full study protocol is available at www.thelancet.com.

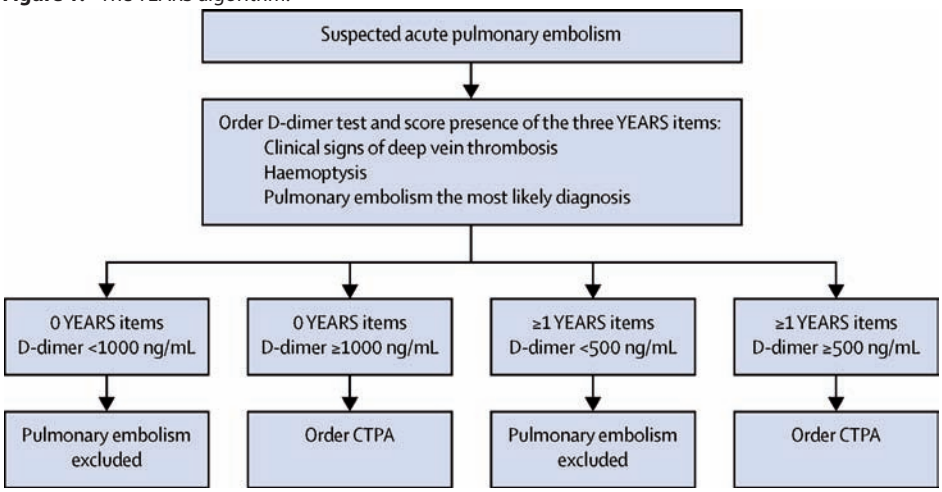
Consecutive outpatients and inpatients with clinically suspected acute (first or recurrent) pulmonary embolism were eligible for inclusion if they were aged 18 years or older. Exclusion criteria were treatment with therapeutic doses of anticoagulants initiated 24 hours or more before eligibility assessment, life expectancy less than 3 months or geographic inaccessibility precluding follow-up, pregnancy, or allergy to intravenous contrast agent. The protocol was centrally approved by the institutional review board of the Leiden University Medical Center, Leiden, Netherlands, which waived the need for informed consent; this decision was endorsed by the local institutional review board of each participating centre.

Procedures

An attending physician who suspected acute pulmonary embolism assessed the patients, and then evaluated the YEARS score by assessing the presence or absence of each of the YEARS items —ie, symptomatic deep vein thrombosis, haemoptysis, and whether pulmonary embolism is the most likely diagnosis— (scored as yes or no) with the pretest probability dependent threshold of the D-dimer test **(Figure 1)**. D-dimer concentrations were measured upon presentation of the patient, according to local practice, with automated well validated high-sensitive quantitative D-dimer assays (Vidas D-dimer Exclusion, Biomerieux, Marcy-L'Étoile, France; Tinaquant, Roche Diagnostica, Mannheim, Germany; STA-LIA, DiagnosticaStago, Asnieres, France; and Innovance, Siemens, Marburg, Germany). Our study reflected daily clinical practice in which D-dimer concentrations are often determined at presentation to the emergency ward. Physicians were not blinded for the D-dimer test result when they assigned the YEARS items.

In patients with no YEARS items and a D-dimer concentration less than 1000 ng/mL, pulmonary embolism was considered excluded and further testing was withheld. In patients with one or more YEARS items and a D-dimer concentration less than 500 ng/mL,

Figure 1. The YEARS algorithm.



Note: PE= pulmonary embolism; DVT= deep vein thrombosis; CTPA=computed tomography pulmonary angiography.

pulmonary embolism was also considered excluded and further testing was withheld. All other patients —ie, either with no YEARS item and a D-dimer concentration of 1000 ng/mL or more, or with one or more items and a concentration of 500 ng/mL or more— were referred for CTPA to show or exclude the diagnosis of pulmonary embolism. The appendix available at www.thelancet.com shows the full CTPA scan protocol. Patients in whom pulmonary embolism was ruled out were left untreated and followed up for 3 months. They were instructed to return to the hospital in the event of symptoms of venous thromboembolism, after which objective diagnostic tests were done to confirm or refute the disease. Follow-up consisted of a scheduled outpatient visit or telephone interview after 3 months. At this visit, information about complaints suggestive of venous thromboembolism was obtained. Patients in whom acute pulmonary embolism was confirmed at baseline were treated with anticoagulants according to international guidelines.

Outcomes

The primary outcome was the 3-month incidence of symptomatic venous thromboembolism in the overall population and in patients managed with and without CTPA separately. The diagnosis of pulmonary embolism or deep vein thrombosis was based on predefined criteria (appendix, available at www.thelancet.com). In case of clinically suspected pulmonary embolism or deep vein thrombosis, objective diagnostic tests were required, including CTPA for suspected pulmonary embolism and compression ultrasonography for suspected deep vein thromboembolism. In case of death, information was obtained from the hospital records. Deaths were classified as caused by pulmonary

embolism if it was confirmed by autopsy, was shown by objective testing before death, or could not be confidently excluded as a cause of death. An independent adjudication committee assessed and adjudicated all suspected venous thromboembolism and deaths during follow-up.

The secondary outcome was the proportion of required CTPA examinations to complete the YEARS algorithm at baseline, as compared post-hoc with the theoretical proportion of CTPA examinations that would have been required if the algorithm, using the two-level Wells' rule outcome and fixed D-dimer threshold of less than 500 ng/mL, would have been applied in the study population and to historical data [20]. Finally, we compared the efficiency to the scenario in which the age-adjusted D-dimer concentration would have been applied (calculated by age ×10 µg/L in patients >50 years). This comparison was done post hoc because the final evidence supporting this approach was not available at the moment of drafting of the protocol [10]. The Wells' rule was calculated by an independent researcher (TvdH) based on the YEARS criteria entered in the case record form and information from the medical charts.

Statistical analysis

On the basis of derivation cohort of the YEARS algorithm, we expected a failure rate of 1.2% in patients managed without CTPA [19]. The sample size was based on this assumption, with the aim to keep the upper limit of the 95% CI of this point estimate below 2.7% [21]. This number reflects the 3-month incidence of venous thromboembolism after normal conventional pulmonary angiography. Any venous thromboembolism incidence with a complete confidence interval below this safety threshold was considered to be safe. We calculated that we needed to include 1333 patients managed without CTPA, with a two-sided α of 5% and a β of 80%. Because 44% of patients in the combined YEARS derivation and validation cohort could have been managed without CTPA and accounting for up to 7.5% loss to follow-up, a total of 3260 patients with suspected pulmonary embolism would be required [19]. For the primary outcome regarding the safety of the diagnostic strategy, we used a per-protocol approach. For the secondary outcome regarding the efficiency of the diagnostic strategy, we used an intention-to-diagnose approach. The difference between approaches was how to report the number of CTPA that were done but not indicated by the strategy. By using this approach, pulmonary embolism diagnosed at presentation on a CTPA that was not indicated was considered as failures of the diagnostic strategy.

For the secondary outcome analysis, we determined the absolute difference in the number of required CTPA examinations between the different clinical scenarios. Finally, we reported outcomes of not predefined post-hoc analyses for relevant subgroups: patients with malignancy, patients 50 years or older, patients with a history of venous thromboembolism, and inpatients and patients with complaints for more than 7 days.

All descriptive parameters and exact 95% CIs around the observed incidences were calculated. All analyses were done with SPSS (version 23). This study is registered with the Netherlands Trial Register, number NTR4193.

Role of the funding source

This study was an academically sponsored trial. The steering committee, consisting of the authors, had final responsibility for the study design, oversight, and data verification and analyses. The sponsor was not involved in the study. All members of the steering committee contributed to the interpretation of the results, approved the final version of the manuscript, and vouch for the accuracy and completeness of the data reported. The final decision to submit the manuscript was made by the corresponding author on behalf of all coauthors.

RESULTS

From Oct 5, 2013, to July 9, 2015, 3616 consecutive patients with clinically suspected pulmonary embolism were screened in the 12 participating hospitals, of whom 151 (4.2%) were excluded (**Figure 2**). **Table 1** summarises the baseline characteristics. Overall, pulmonary embolism was detected in 456 (13%) of 3465 patients: in 55 (3**.**2%) of 1743 patients with none of the YEARS items and 401 (23%) of 1722 patients with one or more YEARS items.

Table 1. Baseline characteristics of patients with suspected pulmonary embolism.

Mean age, years (SD)	53 (18)
Female, n (%)	2154 (62)
Duration of complaints, days (median and IQR)	3 (1-8)
COPD with treatment, n (%)	423 (12)
Heart failure with treatment, n (%)	137 (4.0)
Estrogen use, n (% of women)	337 (16)
Immobilization or surgery in the previous 4 weeks	407 (12)
Outpatient, n (%)	2996 (86)
Heart rate greater than 100/min, n (%)	683 (20)
Previous history of PE or DVT, n (%)	359 (10)
Malignancy, n (%)	336 (9.7)

Note: n=number, SD=standard deviation,COPD=chronic obstructive pulmonary disease.

According to the intention-to-diagnose approach, of the 2946 (85%) patients in whom pulmonary embolism was ruled out at baseline, who remained untreated, and completed the follow-up period, 18 patients were diagnosed with symptomatic venous thromboembolism during 3-month follow-up, with an incidence of 0.61% (95% CI 0.36–0.96). The incidence of fatal pulmonary embolism was 0.20% (six patients, 95% CI 0.07–0.44; **Table 2**). In a worst case scenario, accounting the five patients who were lost to follow-up (four patients had pulmonary embolism excluded without CTPA and one patient had a negative CTPA) as recurrent venous thromboembolism, the 3-month incidence would have been 0.78% (23 of 2951 patients, 95% CI 0.49–1.2). For the per-protocol approach, the failure rate of the diagnostic algorithm was 0.51% (15 of 2943 patients, 95% CI 0.31–0.84) with a 0.20% 3-month risk of fatal pulmonary embolism (six of 2943 patients, 0.08–0.46).

Table 2. Primary outcomes of venous thromboembolism events during 3-month follow-up.

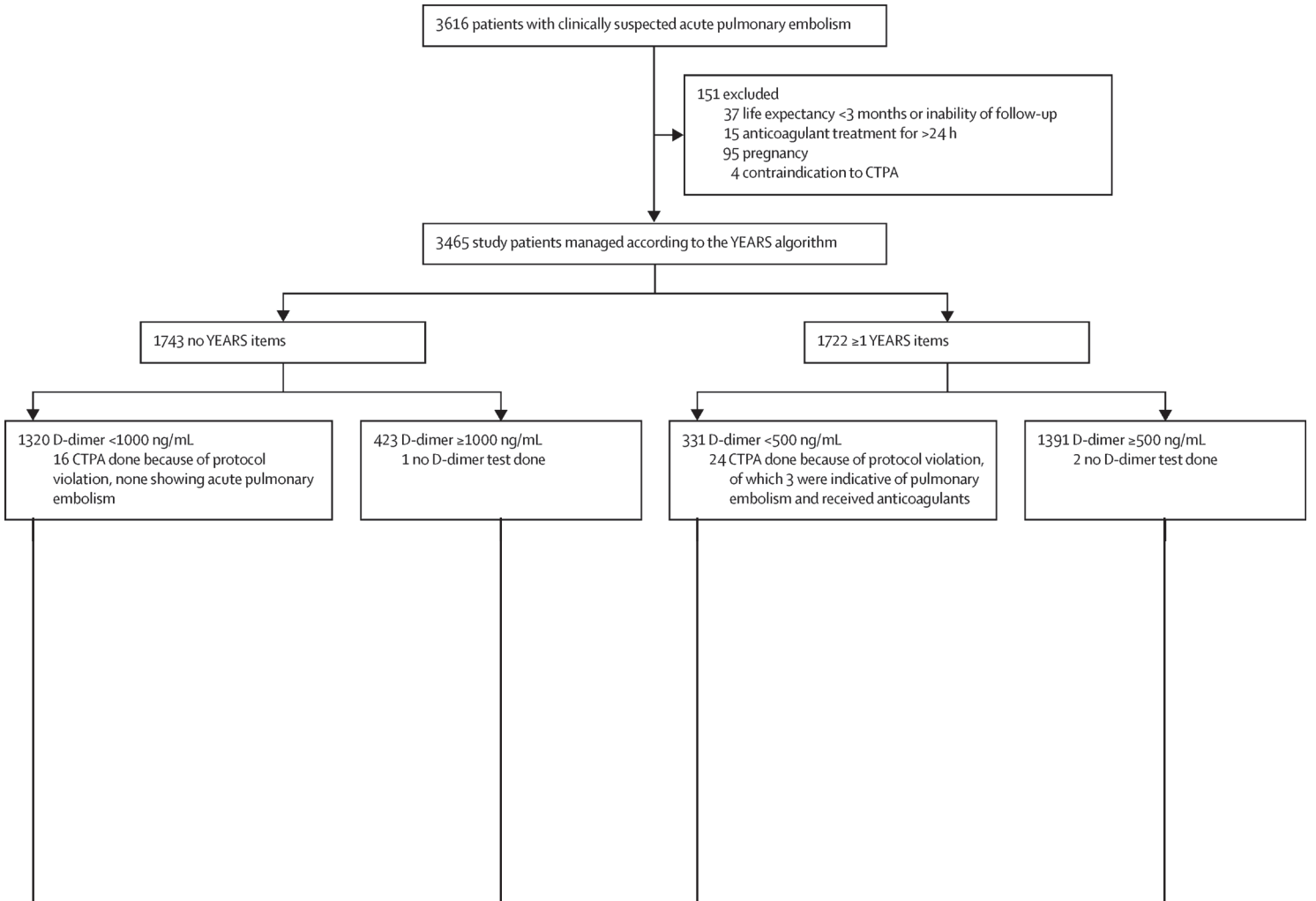
Category	Patients, n	Total VTE, n (%) [95% CI]	Fatal PE, n (%) [95% CI]
Complete algorithm	2946	18 (0.61%) [0.36-0.96]	6 (0.20%) [0.07-0.44]
Patients managed without CTPA	1629	7 (0.43%) [0.17-0.88]	2 (0.12%) [0.01-0.44]
Patients managed with CTPA	1317	11 (0.84%) [0.47-1.5]	4 (0.30%) [0.12-0.78]

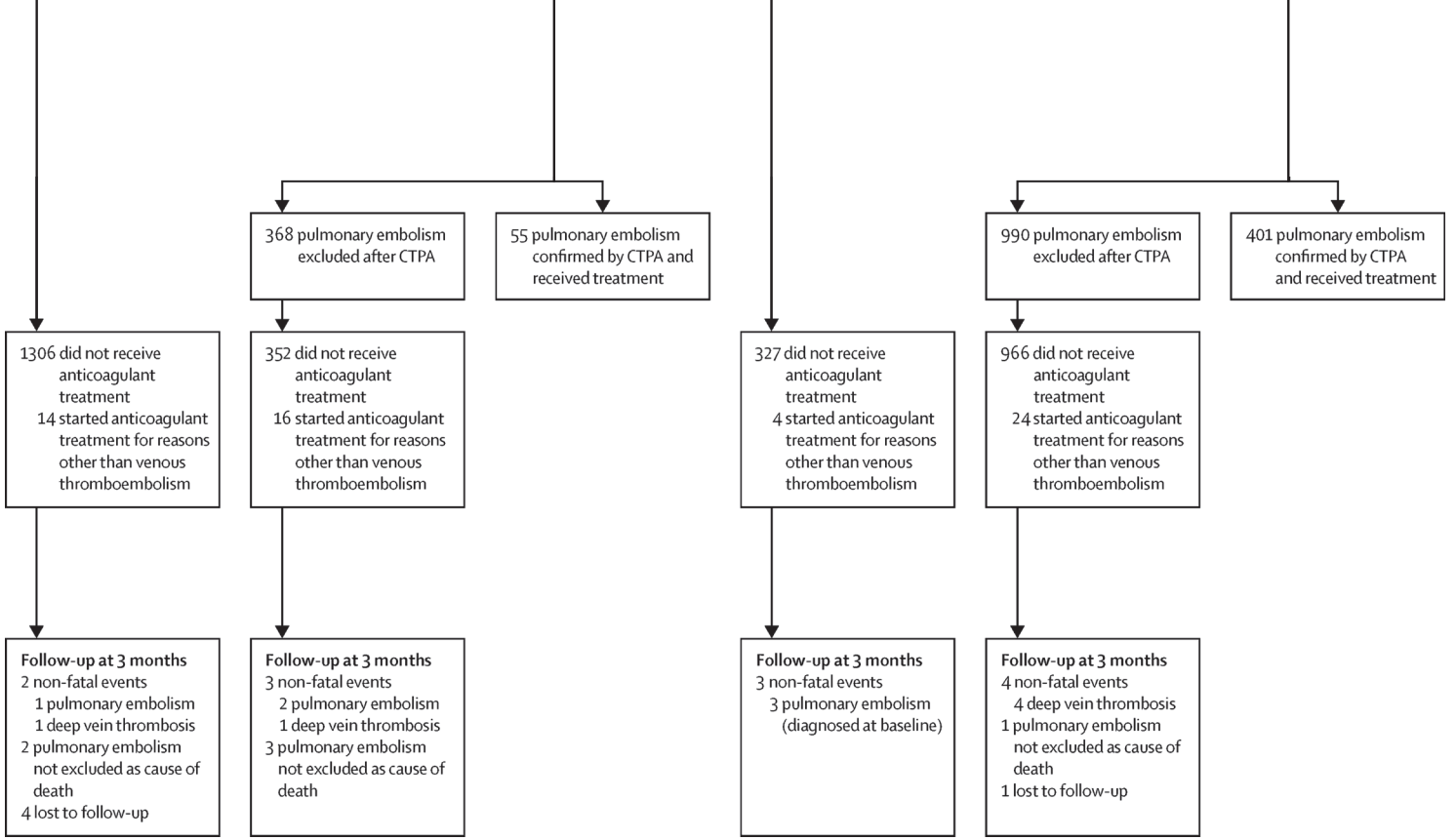
Note: Patients in whom pulmonary embolism was excluded by either a low YEARS score or CT scanning were left untreated. Outcomes calculated for patients who remained untreated and were not lost to follow-up. CTPA=computed tomography pulmonary angiography.

In the intention-to-diagnose approach, CTPA was not done in 1611 (46%) patients and it was not indicated in 1651 (48%) patients following the per-protocol approach. If the standard diagnostic algorithm using Wells' rule and D-dimer with fixed threshold of <500 ng/mL would have been applied, 1174 (34%) patients could have been managed without CTPA at baseline, for an absolute difference of 13% (difference in intention-to-diagnose approach 437 CTPA examinations, 95% CI 10–15%) and 14% (difference in per-protocol approach 477 CTPA examinations, 12–16%) in favour of the YEARS algorithm.

If Wells' rule and the age-adjusted D-dimer threshold would have been applied, 1348 (39**%**) patients could have been managed without CTPA at baseline, an absolute difference of 8.7% (difference in per-protocol approach CTPA examinations 303, 95% CI 6.4–11%) and of 7.6% (difference in intention-to-diagnose approach CTPA examinations 263, 95% CI 5.3–9.9%).

Figure 2. Flowchart of study patients.





Note: PE= pulmonary embolism; DVT= deep vein thrombosis; CTPA= computed tomography pulmonary angiography; [1)]16 CTPA performed due to protocol violation, none showing acute PE; [2)]14 started anticoagulation for other reasons than VTE; [3)]1 no D-dimer test performed; [4)]16 started anticoagulation for other reasons than VTE; [5)]24 CTPA performed due to protocol violation of which 3 were indicative of PE; all three patients were treated with anticoagulants; [6)]4 started anticoagulation for other reasons than VTE; [7)]2 no D-dimer test performed; [8)]24 started anticoagulation for other reasons than VTE.

In the subgroups of patients younger than 50 years and 50 years and older, a 14% absolute reduction in the number of required CTPA examinations was observed when the YEARS algorithm was applied compared with the standard diagnostic algorithm, with failure rates of 0.11% (one of 894 patients, 95% CI 0.02–0.63) and 0.81% (six of 740 patients, 0.37–1.8), respectively. **Table 3** summarises the results for the other subgroups.

Figure 2 shows the management of all 3465 included patients. Of the 1651 patients who should have been managed without CTPA, the protocol was violated in 40 patients. CTPA showed pulmonary embolism in three patients who were treated with anticoagulants. These observations were considered diagnostic failures and are included in the primary outcome. Furthermore, 18 (1.1%) of 1651 patients were treated with oral anticoagulants for other reasons (ie, eight atrial fibrillation, one superficial thrombophlebitis, and nine other reasons including idiopathic pulmonary hypertension and peripheral arterial disease) and four (0.24%) of 1651 patients were lost to follow-up. Four of the remaining 1589 patients returned with symptomatic events of venous thromboembolism (**Table 4**). The 3-month incidence of venous thromboembolism in patients who did not have CTPA according to the YEARS algorithm was 0.43% (seven of 1629 patients, 95% CI 0.17–0.88) and of fatal pulmonary embolism was 0.12% (two of 1629 patients, 0.01–0·44; **Table 2**). Seven other patients (0.43%) died of non-venous-thromboembolism-related causes.

Of the 1358 patients in whom CTPA ruled out pulmonary embolism, 40 patients (2.95%) were treated with anticoagulants for other reasons (ie, 20 atrial fibrillation, three superficial thrombophlebitis, one splanchnic vein thrombosis, one thrombus in the left ventricle, one high-dose thrombosis prophylaxis, one suspected but later ruled out pulmonary vein thrombosis, one vena cava superior syndrome due to mediastinal mass, and 12 other reasons including idiopathic pulmonary hypertension and peripheral arterial disease) and one patient (0.07%) was lost to follow-up. Of the 1317 remaining patients, 11 patients returned with symptomatic events of venous thromboembolism (**Table 5**). The 3-month incidence of venous thromboembolism was 0.84% (11 of 1317 patients, 95% CI 0.47–1.5) and incidence of fatal pulmonary embolism was 0.30% (four of 1317 patients, 0.12–0.78; **Table 2**). 85 other patients (6.5%) died of non-venous-thromboembolism-related causes.

DISCUSSION

Our study showed that the YEARS algorithm safely excluded acute pulmonary embolism. An absolute 14% decrease in the need for CTPA was achieved, compared with the standard algorithm. The 3-month incidence of venous thromboembolism in patients who

Table 3. Diagnostic failures in patients who were managed without CTPA at baseline.

Sex	Age	Years score	Wells score (as calculated post-hoc)	D-dimer, ng/mL	Interval, days	Outcome	Circumstances of outcome event	Adjudicated as
Female	59	0	0	609	54	Death	Developed cardiac arrest during admission for acute severe pancreatitis. Known with myotonic dystrophy type 1 with severe cardiomyopathy and arrhythmias. ICD was earlier deactivated after regular unjustified defibrillations. Resuscitation was unsuccessful	PE not excluded as cause of death
Male	78	0	1	898	11	Death	Diagnosed with end-stage metastasized oropharyngeal carcinoma. Found deceased in nursing home	PE not excluded as cause of death
Female	89	0	1.5	610	18	PE	Subsegmental PE diagnosed on CTPA during admission for pneumonia and acute heart failure related to severe aortic valve stenosis and mitral valve insufficiency. Patient died seven days after treatment was voluntarily withheld	Non-fatal PE
Male	52	0	1	560	49	DVT	DVT 14 days after surgery for glioblastoma multiforme	DVT
Female	21	2	5.5	380	0	PE	CTPA performed due to protocol violation at baseline	Non-fatal PE
Male	58	1	3	420	0	PE	CTPA performed due to protocol violation at baseline	Non-fatal PE
Female	71	1	6	410	0	PE	CTPA performed due to protocol violation at baseline	Non-fatal PE

Note: PE= pulmonary embolism; DVT= deep vein thrombosis; CTPA= computed tomography pulmonary angiography.

Table 4. Diagnostic failures in patients who were managed with CTPA at baseline.

Sex	Age	Years score	Wells score (as calculated post-hoc)	D-dimer, mg/mL	Interval, days	Outcome	Circumstances of outcome event	Adjudicated as
Male	50	0	1.5	1070	34	DVT	Vena cava superior syndrome caused by thrombosis at the site of pacemaker leads	Thrombosis of the vena cava superior
Female	73	0	3	1480	69	Death	Died in hospital under the clinical diagnosis of a pneumonia and acute heart failure	PE not excluded as cause of death
Female	79	0	3	2400	26	PE	Initiation of anticoagulation because of suspected PE without CTPA confirmation after hospital admission because of heart failure and COPD exacerbation	Non-fatal PE
Female	82	0	0	2550	Unknown	Death	Died in nursing home after hospital admission because of acute heart failure and exacerbation of COPD	PE not excluded as cause of death
Female	57	0	1	4170	12	PE	Known with a recurrent sarcoma of the uterus. Subsegmental PE diagnosed postoperatively. Died 33 days after diagnosis of PE during palliative care in a hospice	Non-fatal PE
Female	70	0	1	2400	17	Death	Died after sudden collapse followed by unsuccessful resuscitation 1 day after surgery for gastric carcinoma	PE not excluded as cause of death
Female	73	1	5.5	2500	6	DVT	Known with leukemia. Developed thrombosis of the brachial vein after superficial thrombophlebitis related to an intravenous catheter	DVT
Male	84	1	4	5000	32	DVT	Known with metastasized prostate cancer. Developed DVT after immobilization during admission at the hospital	DVT
Female	66	1	7	1325	43	Death	Known with lung cancer for which curative treatment. Post-radiation stenosis of the trachea for which a stent placed. Died at home after sudden hemoptysis	PE not excluded as cause of death
Male	70	1	3	5000	68	DVT	Subclavian vein thrombus associated with intravenous catheter	DVT
Female	48	1	3	747	78	DVT	Developed DVT and was diagnosed with antiphospholipid syndrome	DVT

Note: PE= pulmonary embolism; DVT= deep vein thrombosis; CTPA= computed tomography pulmonary angiography.

Table 5. Primary endpoint and efficacy in subgroups of the total study population.

				VTE risk during 3 months of follow-up			Efficiency compared to Wells rule in combination with a D-dimer threshold of <500 ng/mL	
Subgroup	**Patients (n)**	**PE at baseline (n, %)**	**Managed without CTPA (n)**	**3-month VTE incidence in patients managed without CTPA events/patients at risk (%; 95%CI)**	**VTE incidence in patients managed with CTPA events/patients at risk (%; 95%CI)**	**Overall VTE incidence after PE was excluded at baseline events/patients at risk % (95%CI)**	**Managed without CTPA (n)**	**Difference with YEARS algorithm n/total % (95%CI)**
Malignancy	336	57 17%	62	2/61 3.2% (0.90-11)	5/211 2.4% (1.0-5.4)	7/272 2.6% (1.3-5.2)	37	25/336 7.4% (5.0-11)
No malignancy	3129	399 13%	1590	5/1573 0.32% (0.14-0.74)	6/1106 0.54% (0.25-1.2)	11/2679 0.41% (0.23-0.73)	1137	453/3129 15% (13-16)
Age < 50 years	1448	126 8.7%	900	1/894 0.11% (0.02-0.63)	1/415 0.24% (0.04-1.4)	2/1309 0.15% (0.04-0.56)	704	196/1448 14% (12-15)
Age ≥ 50 years	2017	330 16%	752	6/740 0.81% (0.37-1.8)	10/902 1.1% (0.6-2.0)	16/1642 0.98% (0.6-1.6)	470	282/2017 14% (13-16)
No history of VTE	3106	349 11%	1529	6/1517 0.40% (0.18-0.86)	10/1193 0.84% (0.46-1.5)	16/2710 0.59% (0.36-0.96)	1120	409/3106 13% (12-14)
History of VTE	359	107 30%	123	1/117 0.85% (0.15-4.7)	1/124 0.81% (0.14-4.6)	2/241 0.83% (0.23-3.0)	54	69/359 19% (15-24)
Inpatient	469	66 14%	200	1/195 0.51% (0.09-2.9)	3/198 1.5% (0.52-4.4)	4/393 1.0% (0.40-2.6)	135	65/469 14% (11-17)
Outpatient	2996	390 13%	1452	6/1439 0.42% (0.19-0.91)	8/1119 0.71% (0.36-1.4)	14/2558 0.55% (0.33-0.92)	1039	413/2996 14% (13-15)
Complaints ≤7 days	2599	362 14%	1266	7/1253 0.56% (0.27-1.2)	9/942 0.96% (0.50-1.8)	16/2195 0.73% (0.45-1.2)	901	365/2599 14% (13-15)
Complaints >7 days	866	94 11%	386	0/381 0% (0-1.0)	2/375 0.53% (0.15-1.9)	2/756 0.26% (0.07-0.96)	273	113/866 13% (11-15)

Note: n=number, CI= confidence interval, CTPA= computed tomography pulmonary angiography, VTE = Venous Thromboembolism.

did not undergo CTPA was in line with that observed in studies using algorithms with sequential diagnostic testing and traditional two-level Wells' score, and a fixed cutoff concentration of D-dimer of 500 ng/mL: 0.43% (95% CI 0.17–0.88) in our study versus 0.34% (0.036–0.96) reported by a meta-analysis [20]. Moreover, the risk of recurrent venous thromboembolism in patients with a normal CTPA was comparable to the risk observed in previous studies using standard algorithms: 0.84% (95% CI 0.47–1.5) versus 1.2% (0.8–1.8) [22]. Additionally, fatal pulmonary embolism occurred in 0.30% (95% CI 0.12–0.78) of patients in our study compared with 0.6% (0.4–1.1) in another study using standard algorithms [22].

The advantage of the YEARS algorithm over existing algorithms is the large reduction in the need for CTPA, which reduces radiation exposure and overdiagnosis,[1-4,23] and is achieved by using variable D-dimer thresholds depending on the clinical probability. This study is the first prospective outcome study that validated a D-dimer threshold of 1000 ng/mL in patients with a low clinical probability.

While our study was ongoing, another strategy to reduce the number of CTPA has been validated in a prospective outcome study: the age-adjusted D-dimer threshold [10]. If this strategy would have been applied to our study population, the YEARS algorithm would have led to an absolute reduction of 8.7% (95% CI 6.4–11) of CTPA. The main reason for this difference is the applicability of the YEARS algorithm to patients with suspected acute pulmonary embolism in all ages, and not only in patients older than 50 years. In patients younger than 50 years, the YEARS algorithm leads to a 14% absolute reduction of CTPA. Of note, reducing the number of CTPA is very relevant for young patients, particularly women, in whom concerns have been raised about long-term effects of radiation on the risk of breast cancer.

Methodological strengths of the study include the large number of consecutive patients, the near complete follow-up, and the independent adjudication of endpoints. Furthermore, by studying a real-world cohort of patients in daily practice, we expect that the YEARS algorithm can be easily implemented outside the participating study sites, and that our data for safety and efficiency are representative for non-trial conditions. Additionally, our results are in line with the numbers reported in the initial derivation and retrospective validation study of our algorithm [19]. Of note, although haemodynamic instability was not a formal exclusion criterion of this study, we have described a cohort of only haemodynamically stable patients.

Limitations of our the study are the absence of a control group because we did not do a randomised study and could therefore not directly compare the risk of venous thromboembolism with a control group that would have been managed with traditional algorithms. However, the low observed 3-month risk of venous thromboembolism and near complete follow-up strongly support the chosen study design. Moreover, although an independent committee evaluated and adjudicated all endpoints, autopsy was

hardly scarcely done. As a consequence, it was difficult to exclude pulmonary embolism as a possible cause of death in six patients during follow-up. These patients already had or developed extensive comorbidity, or went into the final stage of a terminal illness during the follow-up period, with most of them dying in an outpatient setting. Even so, although pulmonary embolism was conservatively adjudicated as the cause of death in these patients, the recurrence rate observed in our study remained well below the safety threshold, reinforcing the validity of our findings. Furthermore, the prevalence of pulmonary embolism was higher than observed in large cohorts in North America, but lower than observed in previous studies in Europe. The study patients were relatively young, but identical to those in an earlier large diagnostic management study by our group [7]. The results of the subgroup analyses, however, confirm the validity of applying the YEARS algorithm in a patient cohort with higher pulmonary embolism prevalence of up to 30% and provide evidence of the generalisability of our findings. Lastly, there were 43 violations of the study protocol, with a D-dimer test not done in three patients and a non-indicated CTPA done in 40 patients, of which three confirmed the presence of acute pulmonary embolism. This number is comparable to that in the Christopher study, in which two of 25 unjustified CTPA examinations revealed pulmonary embolism [7]. Finally, because of the small number of patients with cancer included in our study, the safety of this algorithm for patients with suspected pulmonary embolism in the presence of cancer remains to be determined.

In conclusion, the YEARS diagnostic algorithm safely ruled out acute pulmonary embolism in patients presenting with clinically suspected pulmonary embolism, with a low risk for venous thromboembolism during a 3-month follow-up. The main advantage of the YEARS algorithm is the absolute 14% decrease in the number of CTPA examinations that is applicable to all ages and was shown to be consistent across subgroups.

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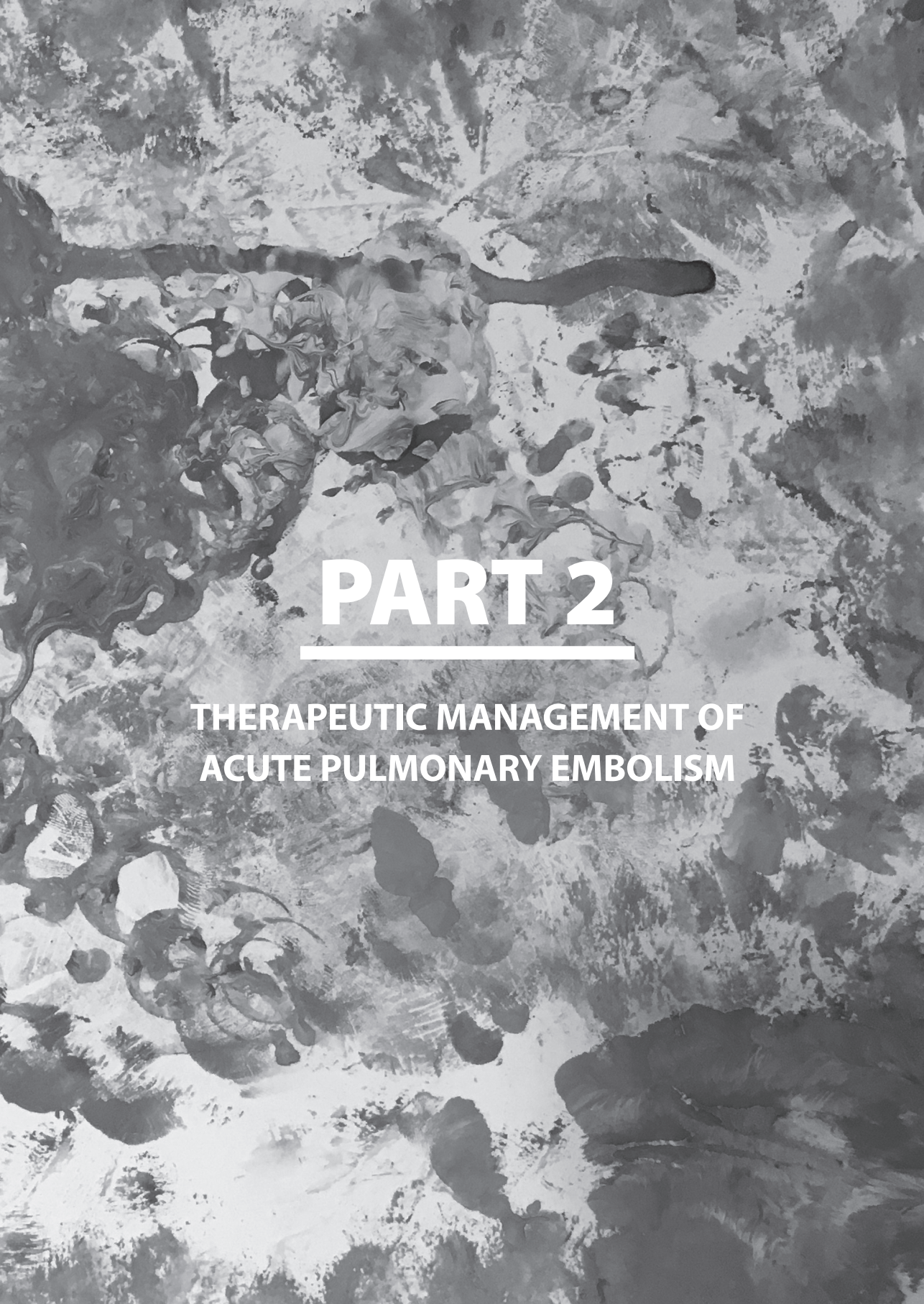

PART 2

THERAPEUTIC MANAGEMENT OF ACUTE PULMONARY EMBOLISM

CHAPTER 7

Effectiveness and safety of novel oral anticoagulants as compared with vitamin K antagonists in the treatment of acute symptomatic venous thromboembolism: a systematic review and meta-analysis

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ABSTRACT

Introduction

New direct oral anticoagulants (NOAC) constitute a novel treatment option for acute venous thromboembolism (VTE), with practical advantages. Individual studies have demonstrated comparable efficacy to that of vitamin K antagonists (VKA) and have suggested a more favorable safety profile. We performed a meta-analysis to determine the efficacy and safety of NOAC as compared with those of VKA in patients with acute VTE.

Methods

We searched MEDLINE, EMBASE, the Cochrane Database of Systematic Reviews and the Clinical Trials Registry up to October 2013. Eligible studies included phase 3 trials comparing NOAC with VKA in patients with acute VTE. Relative risks (RR), absolute risk differences and numbers needed to treat (NNT) to prevent one event were calculated for recurrent VTE, fatal pulmonary embolism (PE), overall mortality, major bleeding, and other bleeding complications, with random-effects models.

Results

Five studies were included, investigating four NOAC (rivaroxaban, dabigatran, apixaban, and edoxaban) in 24 455 patients with acute VTE. RR for recurrent VTE, fatal PE and overall mortality for NOAC vs. VKA were 0.88 (95% confidence interval [CI] 0.74–1.05), 1.02 (95% CI 0.39– 5.96), and 0.97 (95% CI 0.83–1.14), respectively. The RR for major bleeding was 0.60 (95% CI 0.41–0.88). The NNT with NOAC instead of VKA to prevent one major bleed was 149. The RR and NNT for fatal bleeding were 0.36 (95% CI 0.15–0.87) and 1111. A fixed-effect network analysis did not demonstrate significant differences between individual NOAC and rivaroxaban.

Conclusions

NOAC have comparable efficacy to that of VKA, and are associated with a significantly lower risk of bleeding complications, although the NNT to prevent one major bleed was relatively high.

INTRODUCTION

Vitamin K antagonists (VKA) constitute the standard treatment for venous thromboembolism (VTE), which includes acute pulmonary embolism (PE) and deep vein thrombosis (DVT). VKAs are highly effective for the prevention of recurrent VTE, with a relative risk (RR) reduction of ~ 85% as compared with placebo, resulting in a recurrence risk of ~ 3% while patients are on treatment [1]. Two important limitations of VKA treatment are the need for tailored dosing based on frequent International Normalized Ratio monitoring, and the rate of major bleeding complications of ~ 2.1% during the first 6 months of treatment, with a case-fatality rate of 11% [2]. Intracranial bleeding account for 8.7% of major bleeds, and is associated with a mortality risk of ~ 46% [3]. Most major bleeds occur during the first weeks of VKA treatment, presumably because of an underlying bleeding predisposition [3,4].

In recent years, new direct oral anticoagulants (NOAC) have been developed, including factor IIa (thrombin) and FXa inhibitors, which lack some of the limitations of VKA treatment. The relatively stable pharmacokinetics and pharmacodynamics of these agents obviate the need for routine laboratory monitoring [5]. Several trials in patients with acute VTE have demonstrated comparable efficacy to that of VKA in terms of VTE recurrence rates, with lower risks of bleeding complications [6–10]. Nonetheless, the absolute risk of bleeding was low, ranging from 0.6% for fatal bleeding to 10.6% for a first major or clinically relevant non-major bleeding, most differences being non-significant. However, detailed knowledge about bleeding complications is imperative for the use of NOAC in patients with acute VTE. We therefore performed a systematic review and meta-analysis to assess the risks of recurrent VTE and bleeding complications in patients with acute VTE during treatment with NOAC as compared with VKA.

METHODS

Data sources and searches

We searched MEDLINE (via PubMed), EMBASE, the Cochrane Database of Systematic Reviews and the Clinical Trials Registry for peer-reviewed publications comparing NOAC with standard VKA treatment from inception to 25 October 2013. Our strategy included the National Library of Medicine's Medical Subject Headings keyword nomenclature and text words for VTE and NOAC, and validated search terms for randomized controlled trials. The complete search string is detailed in Data S1 (all supplementary files are available at http://onlinelibrary.wiley.com/journal/10.1111/(ISSN)1538-7836/). The electronic search was complemented with a manual review of reference lists of included articles and review articles. For unreported data, we additionally searched the authorization

documents available through the European Medicines Agency (www.ema.europa.eu/ema), and requested the manufacturer to provide unreported data.

Study selection and quality assessment

Search results were combined and duplicates were removed. Studies were screened for relevance by two independent reviewers, on the basis of title and abstract (T.vdH. and P.L.dE.). Discrepancies were resolved by consensus or by contacting a third reviewer (F.A.K.). Fulltext articles identified by either reviewer as potentially relevant were retrieved for further evaluation by the two reviewers. Inclusion criteria for eligible studies were as follows: (i) a phase 3 randomized controlled trial in patients with acute VTE comparing an orally administered direct FIIa inhibitor (including but not limited to dabigatran) or a direct FXa inhibitor (including but not limited to edoxaban, rivaroxaban, and apixaban) with VKA treatment; (ii) concerning a population with objectively diagnosed acute DVT, PE, or both; (iii) randomly allocating patients to the intervention groups; (iv) reporting outcomes after at least 3 months of follow-up, including the diagnosis of acute recurrent VTE based on predefined objective criteria in accordance with current international standards [11] and the rate of both major and clinically relevant non-major bleeding events, and adjudication of outcomes by an independent adjudication committee; and (v) publication in a peer-reviewed journal. Exclusion criteria were as follows: (i) studies concerning ximelagatran, as its use was rejected by the Food and Drug Administration, owing to concerns about potential liver toxicity; and (ii) studies evaluating extended anticoagulant treatment, as a proportion of patients in these studies were also included in the acute-phase studies, and we were only interested in patients with acute VTE, as most bleeding complications occur shortly after the initiation of anticoagulant treatment [3,4].

Risk of bias was evaluated in accordance with the Cochrane Collaboration's tool for assessing risk of bias in randomized trials [12]. This tool evaluates the presence of random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other risks of confounding.

Study outcomes and definitions

Efficacy outcomes were recurrent VTE, fatal PE, and overall mortality. Safety outcomes were major bleeding, non-fatal major bleeding at a critical site, clinically relevant non-major bleeding, non-fatal intracranial bleeding, major gastrointestinal bleeding, and fatal bleeding during anticoagulant treatment.

Recurrent symptomatic VTE included fatal and non-fatal PE and DVT. Recurrent VTE was considered as a cause of death if there was objective documentation in terms of

autopsy, or if death could not be attributed to another documented cause of death and PE could not be ruled out.

The definition of major bleeding was similar for all included studies: overt and associated with a decrease in the hemoglobin level of ≥ 2 g/dL, requiring transfusion of at least two units of blood, occurring in a critical site (intracranial, intraspinal, intraocular, pericardial, intra-articular intramuscular with compartment syndrome, retroperitoneal), or contributing to death [13]. In all included studies, except for the Re-Cover study, clinically relevant non-major bleeding was defined as overt bleeding not meeting the criteria for major bleeding complications, but associated with medical intervention, contact with a physician, interruption of study drug, or discomfort or impairment in carrying out activities in daily life [14]. In the Re-Cover study, several criteria were established for clinically relevant non-major bleeding that are comparable with the definition used in the other trials.

Data extraction

Data extraction was independently performed by two reviewers. For each included study, we extracted the number of participants, follow-up period, number of patients with DVT, PE, or both, unprovoked VTE, active malignancy, previous VTE, and the mean time spent in therapeutic range (TTR) during VKA therapy.

Data synthesis and analysis

Data were analyzed with the Mantel–Haenszel random-effects model, by the use of Review Manager (V. 5.1; The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen). RRs with corresponding 95% confidence intervals (CI) were reported. Comparisons were performed for all endpoints. Statistical heterogeneity was assessed and quantified with the Cochrane Q-test and the I^2-statistic, respectively. Absolute risk differences with CI and the number needed to treat (NNT) with NOAC in order to prevent one outcome event were calculated. The NNT calculation was based on the point estimate of the absolute risk difference. The presence of publication bias was evaluated with funnel plots, with formal tests for funnel plot asymmetry being used only in the case of inclusion of at least 10 studies.

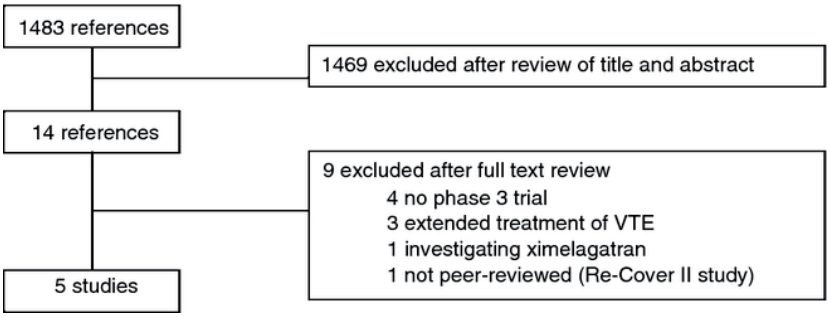
In the absence of trials making direct comparisons between NOAC, we performed a fixed-effect network analysis based on inverse variance weighting. In this analysis, dabigatran, apixaban and edoxaban were compared with rivaroxaban. Rivaroxaban was chosen as the comparator, as this is the only drug currently registered for the treatment of acute VTE.

RESULTS

Study selection

The initial search identified 889 records in PubMed, 453 unique records in EMBASE, 67 unique records in the Cochrane Database of Systematic Reviews, and 74 records from the Clinical Trials Registry, resulting in a total of 1483 references. On the basis of screening of titles and abstracts, 14 studies were selected for full text review. Of these 14 studies, four were excluded because they were not phase 3 trials [12,15–17], the Re-Cover II study was excluded because this study had not yet been published in a peer-reviewed journal [18], the THRIVE II/V study was excluded because of the use of ximelagatran (application rejected by the Food and Drug Administration because of concerns about potential liver toxicity) [19], and three references were excluded because extended treatment of VTE was investigated [20–22]. Therefore, five studies were eligible for inclusion (**Figure 1**) [6–10].

Figure 1. Flow diagram of study selection.



Note: VTE, venous thromboembolism.

Characteristics of included randomized controlled trials

One study evaluated dabigatran in patients with PE and/ or DVT (Re-Cover I study) [6], one investigated rivaroxaban in patients with DVT (Einstein-DVT study) [7], one investigated rivaroxaban in patients with PE (Einstein-PE study) [8], one investigated apixaban in patients with DVT and/or PE (Amplify study) [9], and one investigated edoxaban in patients DVT and/or PE (Hokusai study) [10]. In total, 24 455 patients were included, of whom 57% were male. The mean age ranged between 55 and 58 years. The percentage of patients with unprovoked VTE varied from 62% to 90%. Overall, PE was present in 10 796 patients (44%), and 13 607 (56%) had isolated proximal DVT. Active malignancy was present in 1465 patients (6%), 4651 patients (19%) had experienced a previous VTE, and the TTR ranged from 58% to 64% (**Table 1**). Dabigatran (150 mg twice daily) and edoxaban (60 mg once daily, or 30 mg once daily in the case of a creatinine clearance of 30–50 mL/min or a body weight of < 60 kg) were combined with weight-adjusted therapeutic-dose low molecular weight heparin or unfractionated heparin as initial

Table 1. Study characteristics.

Study Year Drug Class	Treatment duration in months	Patients n	Men n (%)	Mean age in years	PE or PE and DVT n (%)	Isolated DVT n (%)	Unprovoked n (%)	Cancer n (%)	Previous VTE n (%)	TTR in VKA group %
Re-Cover 2009 Dabigatran DTI	6	2539	1484 (58)	55	786 (31)	1749 (69)	Not provided	121 (5)	649 (26)	60
Einstein-DVT 2010 Rivaroxaban FXa inhibitor	3/6/12*	3449	1960 (57)	56	23 (1)	3405 (99)	2138 (62)	207 (6)	666 (19)	58
Einstein-PE 2012 Rivaroxaban FXa inhibitor	3/6/12*	4832	2556 (53)	58	4832 (100)	0 (0)	3117 (65)	223 (5)	944 (20)	63
Amplify 2013 Apixaban FXa inhibitor	6	5395	3167 (59)	57	1836 (34)	3532 (65)	4845 (90)	143 (3)	872 (16)	61
Hokusai 2013 Edoxaban FXa inhibitor	3/6/12*	8240	4716 (57)	56	3319 (40)	4921 (60)	5410 (66)	771 (9)	1520 (18)	64

* Treatment duration defined by treating physician.

Note: DTI: direct thrombin inhibitor; Fxa inhibitor: factor Xa inhibitor; PE: pulmonary embolism; DVT: deep vein thrombosis; VTE: venous thromboembolism; TTR: time in therapeutic range; VKA: vitamin K-antagonists.

treatment for at least 5 days, whereas rivaroxaban (15 mg twice daily for 3 weeks, followed by 20 mg once daily) and apixaban (10 mg twice daily for 7 days, followed by 5 mg twice daily) were used as single-drug regimens. In the Re-Cover study and the Amplify study, patients were treated for 6 months; in the Einstein studies and the Hokusai study, the treating physician determined the treatment duration. In the Einstein-DVT study, 63% of the patients were treated for 6 months, 25% for 12 months, and 12% for 3 months. In the Einstein-PE study, 57% of the patients were treated for 6 months, 37% for 12 months, and 5% for 3 months. In the Hokusai study, 12% of the patients were treated for 3 months, 26% for 3–6 months, and 61% for > 6 months.

All included studies were of good quality as determined by the Cochrane Collaboration's tool for assessing risk of bias in randomized trials (**Figure 2**). Most important potential risks of bias were associated with the open label design of the two Einstein studies [7,8], and all five studies were sponsored and managed by the pharmaceutical industry. As our meta-analysis included only five studies, we did not perform formal tests for funnel plot asymmetry (Data S2).

Figure 2. Results of Cochrane Collaboration's tool for assessing risk of bias.

	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Other bias
Re-Cover 2009	+	+	+	+	+	+	-
Einstein-DVT 2010	+	+	-	+	+	+	-
Einstein-PE 2012	+	+	-	+	+	+	-
Amplify 2013	+	+	+	+	+	+	-
Hokusai 2013	+	+	+	+	+	+	-

Note: key: +: Low risk of bias; -: High risk of bias.

Meta-analysis: efficacy outcomes

During anticoagulant treatment, recurrent VTE occurred in 241 of the 12 151 patients (2.0%) treated with NOAC and in 273 of the 12 153 patients (2.2%) treated with VKA. In accordance with the results of the individual studies, the combined RR for recurrent VTE did not demonstrate a significant difference between these drug classes: 0.88 (95% CI 0.74–1.05) (**Table 2; Figure 3**). Fatal PE occurred in nine of the 12 151 patients (0.07%) treated with NOAC and in nine of the 12 153 patients (0.07%) treated with VKA. In total, 290 of the 12 197 patients (2.4%) treated with NOAC and 298 of the 12 193 patients (2.4%) treated with VKA died during follow-up. The RR for all-cause mortality was 0.97 (95% CI 0.83–1.14). The I^2 of all evaluated efficacy outcomes was 0%, indicating low heterogeneity.

Table 2. Efficacy and safety outcomes.

Outcome	NOAC n % Range	VKA n % Range	Pooled absolute risk difference % 95% CI	NNT with NOACs to prevent 1 event
Recurrent VTE	241/12,151 2.0 1.6-2.4	273/12,153 2.2 1.8-3.0	-0.24 -0.060 to 0.11	417
Fatal PE	9/12,151 0.07 0.04-0.10	9/12,153 0.07 0.00-0.24	0.01 -0.06 to 0.08	10,000
Overall mortality	290/12,197 2.4 1.5-3.2	298/12,193 2.4 1.7-3.1	-0.10 -0.47 to 0.28	1,000
Major bleeding	131/12,197 1.1 0.6-1.6	211/12,193 1.7 1.2-2.2	-0.67 -1.13 to -0.21	149
Non-fatal bleeding at a critical site	28/12,179 0.23 0.08-0.32	77/12,193 0.63 0.18-1.08	-0.38 -0.65 to -0.10	263
Clinically relevant non-major bleeding	806/12,179 6.6 3.9-9.5	1024/12,193 8.4 6.9-9.8	-1.77 -3.40 to -0.15	56
Non-fatal intracranial bleeding	11/12,179 0.09 0.00-0.12	31/12,193 0.25 0.00-0.42	-0.14 -0.31 to 0.03	714
Major gastrointestinal bleeding	28/8,079 0.35 0.17-0.71	43/8,071 0.53 0.23-0.67	-0.16 -0.42 to 0.11	625
Fatal bleeding	7/12,179 0.06 0.04-0.08	21/12,193 0.17 0.07-0.29	-0.09 -0.17 to 0.00	1,111

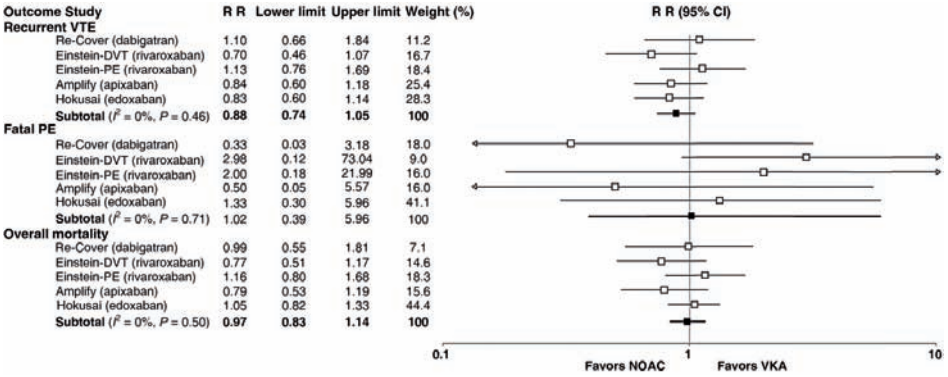
Note: NOAC: new direct oral anticoagulants; VKA: vitamin K-antagonists; NNT: number needed to treat; CI: confidence interval; VTE: venous thromboembolism; PE: pulmonary embolism.

Meta-analysis: safety outcomes

All combined RR were significantly lower for the patients treated with NOAC, except that for major gastrointestinal bleeding (**Table 2; Figure 4**). Major bleeding occurred in 1.1% of the patients treated with NOAC and in 1.7% of the patients treated with VKA, with an accompanying combined RR of 0.60 (95% CI 0.41–0.88) and an I^2 of 62%. The combined absolute risk difference for major bleeding was -0.67% (95% CI -1.13 to -0.21), resulting in an NNT with NOAC instead of VKA of 149 (95% CI 88–476).

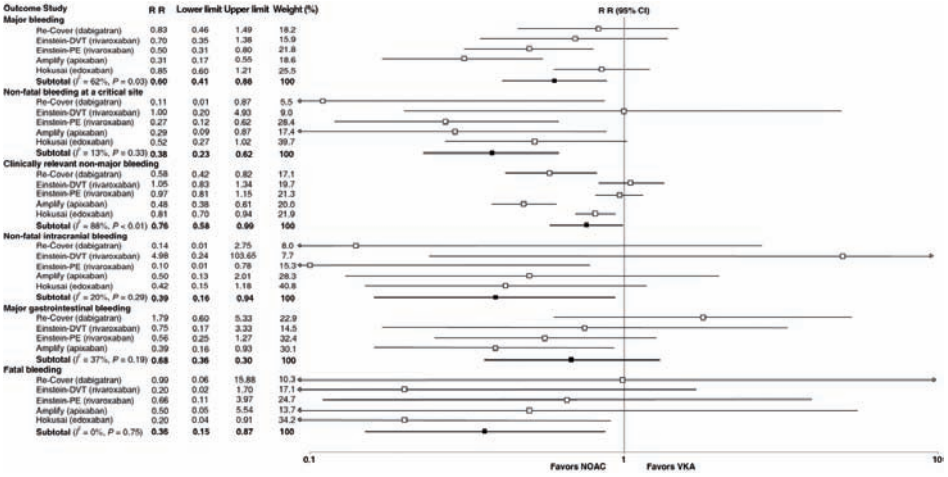
Non-fatal bleeding at a critical site occurred in 0.23% of the patients treated with NOAC and in 0.63% of the patients treated with VKA. The combined RR was 0.38 (I^2 = 13%; 95% CI 0.23–0.62) and the absolute risk difference was -0.38% (95% CI -0.65 to -0.10), resulting in an NNT of 263 (95% CI 153–1000).

Figure 3. Efficacy outcomes.



Note: NOAC: New Direct Oral anticoagulants; VKA: vitamin-K antagonists.

Figure 4. Safety outcomes.



Note: NOAC: New Direct Oral anticoagulants; VKA: vitamin-K antagonists.

The combined RR for clinically relevant non-major bleeding was 0.76 (95% CI 0.58–0.99). This risk varied considerably between the individual studies (I^2 of 88%). In the studies investigating rivaroxaban (Einstein-DVT and Einstein-PE), the RR were very similar, whereas in the studies investigating dabigatran, apixaban, and edoxaban, the RR were in favor of NOAC.

Non-fatal intracranial bleeding occurred in 0.09% of the patients treated with NOAC- and in 0.25% of the patients treated with VKA, resulting in a combined RR of 0.39 (95% CI 0.16–0.94). Only in the Einstein-DVT study was the incidence higher in patients treated with rivaroxaban than in those treated with VKA: two events in 1718 patients vs. 0 in 1711 patients. In the EINSTEIN-PE study, which also evaluated rivaroxaban, the opposite

association was observed. Owing to the low incidence rates of intracranial bleeding and the wide CI, the I^2 was only 20%.

The incidence of major gastrointestinal bleeding was not reported in the Hokusai study, and the combined RR of the other four studies for NOAC was 0.68 (I^2 = 37%; 95% CI 0.36–1.30); only the Re-Cover study, the only study that investigated a direct thrombin inhibitor (dabigatran), reported a higher risk. In this study, the incidence rates were 0.71% (9/1273) in patients treated with dabigatran and 0.39% (5/1266) in patients treated with VKA, a difference of 0.31% (95% CI -0.26 to 0.89).

Fatal bleeding occurred in seven of the 12 179 patients (0.06%) treated with NOACand in 21 of the 12 193 patients (0.17%) treated with VKA, with a combined RR of 0.36 (95% CI 0.15–0.87) and an NNT of 1111 (95% CI 588–0). All studies demonstrated RR in favor of NOAC, with wide CI because of the low incidence rates, resulting in an I^2 of 0%.

Fixed-effect network analysis

In a fixed-network analysis, dabigatran, apixaban and edoxaban were compared with rivaroxaban for the predefined efficacy and safety endpoints. No statistically significant differences were observed for all outcomes. For recurrent VTE, P-values ranged from 0.74 to 0.85, and for major bleeding they ranged from 0.48 to 0.60. The results of the other evaluated outcomes are provided in Data S3.

DISCUSSION

For all of the evaluated efficacy outcomes, the pooled RR were comparable between patients treated with NOAC and patients treated with VKA. In contrast, statistically significantly lower risks were observed for all evaluated bleeding complications during treatment with NOAC than during treatment with VKA, except for the risk of major gastrointestinal bleeding. This is probably attributable to a lack of power, as the Hokusai study did not report major gastrointestinal bleeding separately, and therefore could not be included in this specific analysis. We asked for this information from the manufacturer in vain.

Despite the lower bleeding risk with the new agents, our analyses indicate that the advantage of NOAC in absolute terms is somewhat limited for patients with acute VTE who need anticoagulant treatment for a relatively short duration. This is reflected by the high NNT for treatment with NOAC instead of VKA, ranging from 56 to prevent a clinically relevant non-major bleeding to even 1111 to prevent one fatal bleeding. Although the inclusion criteria of the trials ruled out patients with any bleeding risks, the relatively high NNT cannot be explained by an overall low incidence of bleeding, as the bleeding incidences from the pooled studies are very similar to those of other large VTE treat-

ment studies [3]. Therefore, when NOAC are introduced as a generally accepted therapy for acute VTE, the relatively small net benefit should be weighed against the financial consequences of using this costly drug class.

Last year, the first meta-analysis of the efficacy and safety of NOAC for the treatment of acute VTE was published, with partly overlapping patient cohorts [23]. The major difference between that meta-analysis and our study is the inclusion of relatively small phase 2 trials with shorter durations of follow-up and different NOAC dosages, and studies on ximelagatran by Fox et al [12,19]. By including the recently published trials on apixaban and edoxaban, we exceed their sample size while restricting our analysis to robust data of high quality.

Regarding the extended treatment of VTE, i.e. beyond the treatment during the first 3–6 months, the efficacy and safety of NOAC as compared with VKA are still unclear. In only one study was dabigatran randomly compared with VKA during extended treatment; hazard ratios for recurrent VTE of 1.44 (95% CI 0.78–2.64) and 0.54 (95% CI 0.41–0.71) for major or clinically relevant non-major bleeding were reported [21]. In two other studies, apixaban and rivaroxaban were randomly compared with placebo and were included in a recently published meta-analysis [24]. As expected, these drugs showed high efficacy as compared with placebo, but their efficacy and safety as compared with VKA remain to be demonstrated.

Given the absence of the possibility of direct comparisons between the individual NOAC, we performed an indirect comparison of dabigatran, apixaban and edoxaban with rivaroxaban. Although differences in efficacy and safety outcomes between individual drugs can be reasonably expected, no significant differences in efficacy and safety outcomes were observed. Owing to the relatively low incidence rates of all outcomes, large randomized controlled trials in > 20 000 patients would be required to identify potentially relevant differences between the NOAC. For practical reasons, it seems very unlikely that such studies will be initiated in the (near) future. Therefore, pooling the results of all separate studies evaluating different NOAC in comparison with VKA provides the best available evidence for deciding whether NOAC constitute a suitable alternative, or are even preferable, to VKA for the treatment of acute VTE.

Although not identified by the fixed-effect network analysis, reasonably expected differences between the individual drugs may be the reason for the high heterogeneity observed for major bleeding (I^2 = 62%) and clinically relevant non-major bleeding (I^2 = 88%).

Considering major bleeding, all studies demonstrated RR in favor of NOAC, but the effect size differed. For clinically relevant non-major bleeding, in particular, the RRreported in the Einstein studies differed from the other RR. This might be explained by a specific effect of rivaroxaban, or it could be a result of the PROBE design of the Einstein studies, as the other studies were double-blind studies. For major gastrointestinal bleeding, the

relatively high heterogeneity ($I^2 = 37\%$) seems to be explained by the higher RR reported in the Re-Cover study. This might be explained by an individual drug effect or a difference between drug classes (FIIa inhibitors and FXa inhibitors).

The more favorable safety profile of NOAC may be ascribed to their more stable anticoagulant effect than that of VKA [5]. The lower risk of intracranial bleeding may be a consequence of maintaining normal concentrations of FVII and the formation of FVIIa–tissue factor complexes, which play an important role in cerebral vascular damage [25]. Other supposed mechanisms are the reduced suppression of thrombin at the site of cerebral injury, and the inability of rivaroxaban to substantially penetrate the blood–brain barrier [26].

A concern regarding NOAC is the absence of specific antidotes. On the basis of experimental studies, non-specific prohemostatic agents are recommended for direct reversal of the anticoagulant effect [27,28]. It is of note that patients with a major bleed while on dabigatran had a better prognosis than patients with a major bleed while on VKA[29]. Furthermore, the lower bleeding risk and the presumed introduction of specific antidotes in the coming years put this concern in perspective.

Our study has limitations. First, because of the absence of studies comparing the same drugs, we were unable to perform a random-effects Bayesian network meta-analysis. Even so, the alternatively performed fixed-effect network analysis did not demonstrate significant differences between the individual drugs. Second, we were unable to perform subgroup analyses for patients with PE and DVT. Third, we could not differentiate between early and late bleeding occurrences, as detailed data were lacking. Fourth, treatment durations were not identical throughout the studies, although most patients were subjected to a 6-month anticoagulant course. Fifth, in the Hokusai study, the safety outcomes of fatal PE and overall mortality were only reported for the total follow-up duration. Sixth, the results of this meta-analysis should not be generalized to all patients with acute VTE, as specific populations, including the elderly, patients with cancer, patients with renal insufficiency, patients with rare localizations of VTE (e.g. distal DVT, splanchnic thrombosis, and cerebral vein thrombosis), and patients with morbid obesity, were underrepresented or excluded. Finally, two studies had a PROBE design, in which participants and researchers were aware of the treatment allocation, and only the adjudication committee was blinded. It has been suggested that the open design of PROBE studies leads to a more real-world study population, owing to the easier recruitment of patients, although the risk of reporting bias might be increased. Furthermore, this design may influence decisions regarding other medical treatments. Hence, it has been suggested that the PROBE design could result in overoptimistic results in favor of NOAC. Even so, recent studies evaluating NOAC in patients with atrial fibrillation or VTE have not demonstrated such an effect [30,31].

In conclusion, NOAC show comparable efficacy to VKA in patients with acute VTE, as well as greater practical simplicity and a more favorable bleeding profile, although the absolute benefit was somewhat limited, owing to the high NNT.

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CHAPTER 8

Recurrence risk after anticoagulant treatment of limited duration for late, second venous thromboembolism

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ABSTRACT

Patients with a second venous thromboembolism generally receive anticoagulant treatment indefinitely, although it is known that the recurrence risk diminishes over time while the risk of hemorrhage persists with continued anticoagulation and increases with age. Based on these arguments and limited evidence for indefinitely prolonged treatment, the Dutch guidelines recommend considering treatment of a limited duration (i.e. 12 months) for a 'late' second venous thromboembolism, defined by a second venous thromboembolism diagnosed more than 1 year after discontinuing treatment for a first event. It is hypothesized that the risk of continued anticoagulation might outweigh the benefits in such circumstances. We evaluated this management in daily practice.

Since 2003, limited duration of treatment was systematically considered at our hospital in consecutive patients, in whom we determined the recurrence risk. Of 131 patients with late second venous thromboembolism, 77 were treated for a limited duration, of whom 26 developed a symptomatic third venous thromboembolism thereafter during a cumulative follow-up of 277 years, resulting in an incidence rate of 9.4/100 patient-years (95% confidence interval: 6.1–14). The incidence rates in patients with unprovoked and provoked venous thromboembolism were 12/100 patient-years (95% confidence interval: 7.4–19) and 5.6/100 patient-years (95% confidence interval: 2.2–12), respectively [adjusted hazard ratio 2.8 (95% confidence interval: 1.1–7.2)].

The recurrence risk after treatment of limited duration for 'late' second venous thromboembolism exceeded the risk of hemorrhage associated with extended anticoagulation. Most patients may, therefore, be better served by treatment of indefinite duration, although the risk-benefit ratio of extended anticoagulation should be weighed for every patient.

INTRODUCTION

The optimal duration of treatment for a first episode of venous thromboembolism (VTE), whether deep vein thrombosis (DVT) or pulmonary embolism (PE), has been studied and debated extensively. In general, 3 months of anticoagulant treatment is recommended for patients with a provoked VTE. For those with an unprovoked VTE, it is recommended that treatment lasts at least 3 months, after which the patient should be evaluated for the risk-benefit ratio of extended therapy [1]. In contrast to the numerous studies evaluating the optimal duration of treatment for a first VTE, only one study has evaluated the optimal duration of treatment for a second VTE [2]. In that study, a cumulative VTE recurrence rate of 21% was reported during 4 years of follow-up in patients treated for 6 months, in contrast to a rate of 2.6% in patients in whom treatment was continued [relative risk 8.0; 95% confidence interval (CI): 2.5–26]. As expected, a limited duration of treatment resulted in a lower cumulative incidence of major hemorrhage (2.7% versus 8.6%; relative risk 0.3; 95% CI: 0.1–1.1).

Mainly based on this study, the Dutch multidisciplinary guidelines on the diagnosis and treatment of VTE suggests an indefinite duration of treatment for a second VTE, without making a distinction between provoked and unprovoked VTE [American College of Chest Physician (ACCP) level of evidence 2B] [3].

The guidelines also suggest considering a limited duration of treatment of 12 months for a 'late' second VTE in patients with a long interval between cessation of anticoagulant treatment for the first VTE and the second VTE (ACCP level of evidence 2C). A long interval was arbitrarily defined as a period of more than 12 months. The rationale for the latter recommendation is that patients with a late second VTE have a relatively limited risk of recurrent VTE, which is supported by indirect evidence that the risk of VTE recurrence is highest shortly after cessation of anticoagulant treatment for a first VTE and then rapidly decreases [4,5]. Taking into account that the anticoagulant-associated risk of hemorrhage persists while anticoagulant treatment is continued and considerably increases with age, it is argued that the risk of hemorrhage associated with long-term anticoagulant treatment may outweigh the reduction of risk of recurrent VTE associated with continued anticoagulant treatment in such circumstances [6].

In accordance with the Dutch multidisciplinary guidelines, a limited duration of treatment of 12 months has been systematically considered in all patients diagnosed with a late second VTE since 2003 in the Department of Thrombosis and Hemostasis of our hospital. As this recommendation is supported by only limited evidence, its evaluation is essential. We, therefore, report the results of applying this recommendation in daily clinical practice.

METHODS

We included all consecutive patients who were diagnosed with a late second VTE in the period 2003–2012 in the Department of Thrombosis and Hemostasis of the Leiden University Medical Center (LUMC), Leiden, the Netherlands in a prospective registry. Specific inclusion criteria for the current analysis were: (i) a previously documented symptomatic first provoked or unprovoked VTE; (ii) a documented symptomatic second provoked or unprovoked VTE, and (iii) more than 1 year between cessation of anticoagulant treatment for the first VTE and the diagnosis of the second VTE.

In our hospital, suspected recurrent VTE is managed by using an algorithm starting with determination of pretest probability, followed by either D-dimer and or radiological imaging tests if indicated. The radiological criteria for diagnosing ipsilateral recurrent DVT are a compression ultrasonography that shows incompressibility of a different venous segment than at a reference examination or, in the case of a pronounced increase in vein diameter (≥4 mm), of a previous non-compressible venous segment [7].

The treatment protocol recommended a limited duration of treatment for a late second VTE in the absence of another indication for anticoagulant treatment, but the final decision was made by the treating physician during the first visit of the included patients at our outpatient clinic, approximately 6 weeks after the diagnosis of the second VTE. Patients were rarely tested for hereditary thrombophilic factors, and no standardized model for predicting recurrence risk was used. Diagnostic procedures in the case of suspected recurrence were applied in a standard manner, in accordance with the national and international guidelines [1,3]. For all patients, follow-up was completed for at least 2 years or until March 2014, the patient's death or the primary endpoint was reached. The ethics committee of the LUMC approved this study and waived the requirement for informed consent since the study evaluated standard clinical practice.

The primary endpoint of the analysis was a symptomatic third DVT and/or PE during follow-up, demonstrated by objective diagnostic tests according to the guidelines [1,3,7]. The secondary outcome was the risk of major hemorrhage, defined according to the International Society of Thrombosis and Haemostasis criteria [8].

Provoked VTE was defined as VTE occurring after major surgery or immobilization for at least 3 days within 4 weeks preceding the diagnosis, in a patient with active malignancy (a diagnosis of cancer within 6 months prior to enrolment, any treatment for cancer within the previous 6 months, or recurrent or metastatic cancer), after a recent long flight (>4 hours), during pregnancy or the peripartum period and in patients taking oral contraceptives or hormone replacement therapy. Unprovoked VTE was defined as VTE occurring without any of these provoking factors. Patients were classified according to whether they received treatment of a limited duration, defined as treatment for 12 months or less, or treatment of indefinite duration. Incidence rates of the primary and

secondary endpoints were calculated and the Kaplan-Meier life table method was used to estimate the cumulative event rate.

A Cox proportional hazard model was used to calculate hazard ratios (HR) for clinical characteristics. We performed subpopulation analyses for: (i) patients with unprovoked and provoked second VTE; (ii) patients with unprovoked first and second VTE and those with provoked first and second VTE; (iii) DVT or PE as the second VTE; (iv) patients <65 years old and those ≥65 years old; (v) patients with an anticoagulant effect within the therapeutic range for <60% and ≥60% of the time, calculated by the Rosendaal method [9,10]; and (vi) a limited duration of treatment for the second VTE of 12 months and less than 12 months. Hazard ratios were adjusted for age, sex, type of the second VTE (DVT or PE±DVT) and whether the second VTE was provoked or unprovoked. Analyses were performed using SPSS version 20 (SPSS inc., Chicago, IL, USA).

RESULTS

Between 2003 and 2012, 131 patients were diagnosed with a late second VTE. One patient was excluded from the analysis, because she died before the planned cessation of anticoagulant treatment after 12 months. The baseline characteristics of the whole cohort are shown in **Table 1**.

Limited duration of treatment

Overall, 77 patients were treated for a limited duration: five patients for a total of 3 months, 26 patients for 6 months and 46 patients for 12 months. All these patients were followed up for at least 2 years with a median duration of follow-up of 34 months after treatment cessation. The mean age at the time of diagnosis of the second VTE was 52 years, and 35 patients were male (46%).

In 50 patients (65%) the second VTE was a DVT, leaving 27 patients (35%) diagnosed with PE as the second VTE, with or without symptomatic DVT. The type of the first VTE and second VTE was different in only 15 patients, while in the other 62 patients both events were of the same type. In 46 patients both the first and second VTE were DVT, in 29 (63%) cases the recurrent DVT was ipsilateral to the first, whereas in 17 (37%) cases the second DVT was contralateral to the first. The median time between the first and second VTE was 7.2 years (interquartile range, 3.6 – 13 years). A provoking risk factor for the second VTE was reported for 30 of 77 patients (39%): recent surgery and/or immobilization in 14 patients, oral contraceptive use in eight patients (one of whom also had a history of recent surgery and/or immobilization), a long flight in five patients (one of whom was also taking an oral contraceptive), pregnancy in four patients and malignancy in one patient, leaving 47 patients (61%) with unprovoked, late second VTE.

Table 1. Baseline characteristics.

Characteristic	Total cohort n=131 (%)	Limited treatment n=77 (%)	Indefinite treatment n=54 (%)
Mean age (SD)	53 (16)	52 (15)	54 (16)
Male sex	62 (47)	35 (46)	27 (50)
Known heart failure	3 (2.3)	2 (2.6)	1 (1.9)
Known COPD	4 (3.1)	2 (2.6)	2 (3.7)
Type of first VTE			
DVT	86 (66)	57 (74)	29 (54)
PE ± DVT	45 (34)	20 (26)	25 (46)
Unprovoked first VTE	58 (44)	33 (43)	25 (46)
Type of second VTE			
DVT	87 (66)	50 (65)	37 (69)
PE ± DVT	44 (34)	27 (35)	17 (31)
Unprovoked second VTE	80 (61)	47 (61)	33 (61)
Concordant versus discordant type (regarding the first and second VTE)			
2 times DVT, ipsilateral	45 (34)	29 (38)	16 (30)
2 times DVT, contralateral	27 (21)	17 (22)	10 (19)
2 times PE	30 (23)	16 (21)	14 (26)
1 DVT and 1 PE	29 (22)	15 (19)	14 (26)
Provoked second VTE	51 (39)	30 (39)	21 (39)
Surgery or immobilization	21 (16)	14 (18)	7 (13)
Oral contraceptive use	11 (8.4)	8 (10)	3 (5.6)
Long flight	8 (6.1)	5 (6.5)	3 (5.6)
Pregnancy	7 (5.3)	4 (5.2)	3 (5.6)
Active malignancy	11 (8.4)	1 (1.3)	10 (19)
Median time between first and second VTE in years (IQR)	6.2 (3.3-12)	7.2 (3.6-13)	5.8 (3.2-10)
1-5 years	55 (42)	31 (40)	24 (44)
5-10 years	35 (27)	18 (23)	17 (31)
>10 years	41 (31)	28 (36)	13 (24)
Treatment duration in months			
3	NA	5 (6.5)	NA
6	NA	26 (34)	NA
12	NA	46 (60)	NA
Time in therapeutic range*			
<60%	NA	6/67 (9.0)	NA
≥60%	NA	61/67 (91)	NA

Note: SD: standard deviation; COPD: chronic obstructive pulmonary disease; VTE: venous thromboembolism; DVT: deep vein thrombosis; PE: pulmonary embolism; IQR: interquartile range; NA: not applicable; *only available from 67 patients due to 10 patients who were treated by a Thrombosis Service in another region.

The patient with cancer received the last dose of chemotherapy for testicular cancer at the moment of the second VTE, after which he was in complete remission, allowing treatment cessation according to the Dutch guidelines.

Five patients (6.5%) were treated for only 3 months based on the argument that the late recurrent event was caused by a transient provoking factor, 26 patients (34%) were treated for 6 months and the majority of the 46 patients (60%) were treated for 12 months after the diagnosis of late second VTE. Seven patients (9.1%) died during the follow-up after cessation of anticoagulation. Six of the deaths were not related to VTE: two patients had end-stage metastatic malignancy diagnosed during follow-up, one patient committed suicide, one patient developed non-anticoagulation-associated intracranial bleeding, one patient had end-stage heart failure and one patient died as a direct result of a traffic accident. The cause of death could not be retrieved for one patient, who died at the age of 91, 6 years after cessation of anticoagulant treatment for recurrent DVT.

Overall, 26 of the 77 patients were diagnosed with a third VTE during a cumulative follow-up of 277 patient-years. The third VTE was of the same type as the second VTE in 24 patients: of the 16 patients who developed DVT as the third VTE event, only one had PE as the second VTE and of the ten patients with PE as the third VTE only one had DVT as the second VTE. Of the 16 patients who developed DVT as the third VTE, 12 (75%) had been previously diagnosed with DVT on the same side (either as first or second VTE). Seven of the 26 patients had a provoked second VTE, of whom two patients (29%) experienced a provoked third VTE and five (71%) an unprovoked third VTE. The remaining 19 patients had an unprovoked second VTE: in four cases (21%) the third VTE was provoked, whereas in the other 15 (79%) the third VTE was also unprovoked.

The incidence rate of a third VTE after limited treatment was 9.4 per 100 patient-years (95% CI: 6.1–14), and 1-, 2-, 3- and 5-year cumulative VTE rates were 15% (95% CI: 3.1–34), 19% (95% CI: 6.1–38), 25% (95% CI: 10–42) and 33% (95% CI: 18–49), respectively. When the unexplained death was considered as attributable to recurrent VTE, the incidence rate was 9.7/100 patient-years (95% CI: 6.4–14).

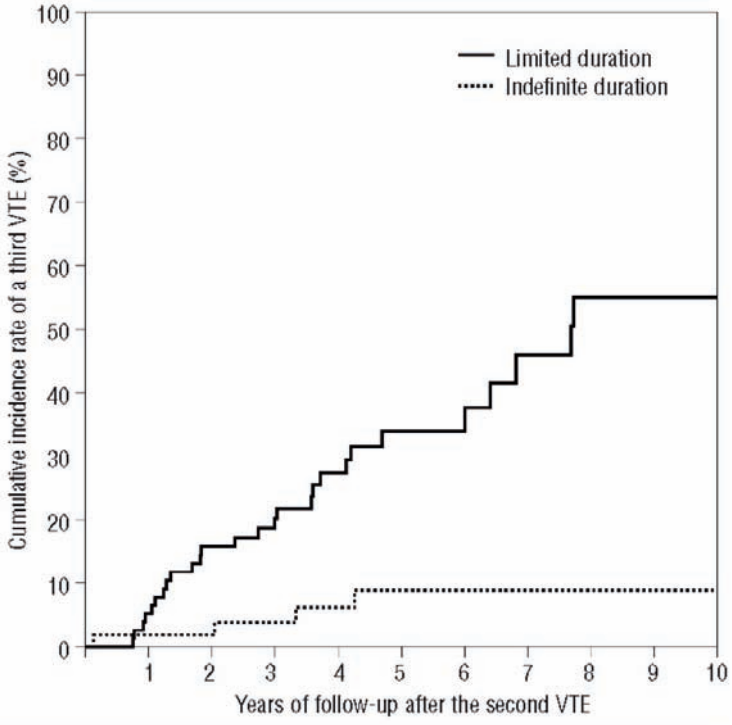
Treatment of indefinite duration

For 39 of the 54 patients who were treated for an indefinite duration, the reason for this decision was documented: ten patients (19%) had an active malignancy, ten patients (19%) had known hereditary thrombophilia, nine patients (17%) had an additional indication for anticoagulant treatment, in four patients (7.4%) it was the patients' strong preference to continue treatment, in four patients (7.4%) antiphospholipid syndrome was diagnosed, one patient (1.9%) was persistently immobile, one patient (1.9%) had a strongly positive family history and in one patient (1.9%) the large thrombotic load of the second VTE was considered as a reason for continuing treatment. For the remaining 15 patients (28%), no specific reason was documented.

Among the patients on anticoagulant treatment for an indefinite period, 13 died during follow-up (24%): in 11 of these patients, VTE was ruled out as the cause of death, whereas the cause of death could not be retrieved for the other two patients.

Four patients developed a third VTE while being treated with anticoagulants during a cumulative follow-up of 332 patient-years, resulting in an incidence rate of 1.2/100 patient-years (95% CI: 0.33–3.1) (**Figure 1**). None of these events was fatal. When the unexplained deaths were considered as attributable to recurrent VTE, the incidence rate was 1.8/100 patient-years (95% CI: 0.66–3.9). Major hemorrhage occurred in eight patients, resulting in an incidence rate of 2.4/100 patient-years (95% CI: 1.0–4.7). None of these hemorrhages were fatal.

Figure 1. Cumulative incidence rate of a third venous thromboembolism in patients treated for a limited duration and patients treated for an indefinite duration.



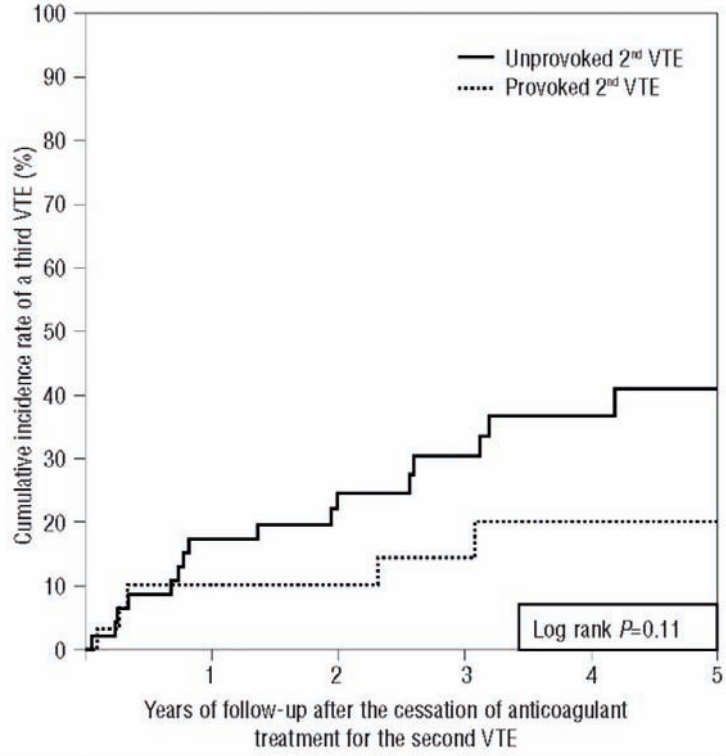
Treatment group	Follow-up in years	1	2	3	4	5	6	7	8	9	10
Limited duration	nrVTE	4	12	15	19	22	23	25	27	27	27
	PAR	73	63	51	38	27	17	12	12	7	4
Indefinite duration	nrVTE	1	1	2	3	4	4	4	4	4	4
	PAR	52	50	45	35	31	29	26	18	11	7

Note: nrVTE: number of recurrent VTE; PAR: patients at risk. Follow-up started at the time of the second venous thromboembolism diagnosis for both categories.

Subgroup analyses in the patients treated for a limited duration

Cox-regression analysis demonstrated a higher risk of recurrence in patients with an unprovoked second VTE than in those with a provoked second VTE (adjusted HR 2.8; 95% CI: 1.1–7.2) (**Figure 2**). The incidence rate in patients with a provoked second VTE was 5.6/100 patient-years (95% CI: 2.2–12). The 1-, 2-, 3- and 5-year cumulative VTE rates were 10% (95% CI: 0.082–48), 10% (95% CI: 0.082–48), 14% (95% CI: 0.54–49) and 20% (95% CI: 1.8–53), respectively. The incidence rate in patients with an unprovoked second

Figure 2. Cumulative third venous thromboembolism event rate in patients with a provoked second VTE versus an unprovoked second VTE, treated for a maximum of 12 months.



Subgroup	Follow-up in years	1	2	3	4	5
Provoked second VTE	nrVTE	3	3	4	5	5
	PAR	25	21	15	12	10
Unprovoked second VTE	nrVTE	8	11	13	15	16
	PAR	38	30	22	15	9

Note: nrVTE: number of recurrent VTE; PAR: patients at risk. Follow-up started at the time of cessation anticoagulant treatment.

VTE was 12/100 patient-years (95% CI: 7.4–19). The 1-, 2-, 3- and 5-year cumulative VTE rates were 17% (95% CI: 3.0–42), 25% (95% CI: 7.8–46), 30% (95% CI: 13–51) and 41% (95% CI: 22–59), respectively. In patients with both an unprovoked first and second VTE the incidence rate of a third VTE was 8.7/100 patient-years (95% CI: 3.5–18) whereas in those with a provoked first and second VTE it was 4.6/100 patient-years (95% CI: 1.3–12).

In patients with DVT as the second VTE, the incidence rate of a third recurrence was 8.3/100 patient-years (95% CI: 4.8–14). In patients with PE as the second VTE, the incidence rate was 12/100 patient-years (95% CI: 5.6–21). This difference between the two groups was not statistically significant (adjusted HR 0.65; 95% CI: 0.29–1.5). The incidence rate of a third VTE in patients <65 years old was 9.9/100 patient-years (95% CI: 6.1–15) whereas in those ≥65 years old it was 7.8/100 patient-years (95% CI:2.5–18), with an adjusted HR of 1.2 (95% CI: 0.43–3.4). Due to the low number of patients whose anticoagulation was in the therapeutic range for <60% of the time, we refrained from subgroup analyses based on this variable (**Table 1**). Finally, the VTE incidence rate in patients treated for 3 or 6 months was lower - although non-significantly - than that after a 12-month treatment period: 6.1/100 patient-years (95% CI: 2.8–12) versus 13/100 patient-years (95% CI: 7.7–21), with an adjusted HR of 0.6 (95% CI: 0.25–1.4).

DISCUSSION

We evaluated the outcome in daily clinical practice of following the recommendation in the Dutch multidisciplinary guidelines to consider a limited duration of treatment in selected patients with a 'late' second VTE [3]. We found a VTE incidence rate of 9.4/100 patient-years after cessation treatment of a limited duration, with a cumulative VTE rate of 15% after 1 year follow-up which increased to 33% after 5 years of follow-up. In order to weigh these results, two issues should be discussed.

First, the VTE incidence rate of 9.4/100 patient-years largely exceeds the risk of major hemorrhage associated with long-term anticoagulant treatment, which was estimated to be 2.7/100 patient-years in a meta-analysis and was 2.4/100 patient-years in our cohort of patients who were treated for an indefinite period [11]. Notably, the clinical impacts of recurrent VTE and major hemorrhage are frequently considered as equivalent, which is supported by the more or less comparable case-fatality rate varying from 3.8 to 11% for recurrent VTE and 9.1% (95% CI: 2.5–22) for major hemorrhage [11-13].

Second, we should compare our results to the 3–4% per year risk of recurrent VTE after a first VTE related to a transient provoking factor, since a limited duration of treatment is generally accepted for these patients [1,14]. The results of our subgroup analyses suggest that patients with a provoked second VTE have a much lower risk of recurrence than have patients with an unprovoked second VTE. Despite the wide confidence interval,

the incidence rate of 5.6/100 patient-years (95% CI: 2.2–12) for a third VTE in patients with a provoked, late second VTE is relatively low and seems to approximate the risk of recurrent VTE after a first provoked VTE.

Based on these considerations, we argue that most patients with a late second VTE are generally better served by treatment of an indefinite duration. Furthermore, our results suggest that selecting patients with a relatively low VTE recurrence risk based on the interval between cessation of anticoagulant treatment and the second VTE is not an appropriate strategy. Nevertheless, it remains essential to weigh the risk-benefit ratio of extended anticoagulant treatment in every patient individually.

The introduction of new oral anticoagulants for the treatment of VTE must be considered in the context of our results, since these drugs are associated with a lower risk of bleeding complications than vitamin K antagonists, and yet have comparable efficacy [15]. The use of these drugs may, therefore, shift the risk-benefit ratio of long-term anticoagulant treatment in favor of indefinite duration of treatment for many patients.

The strengths of our study are the completeness of the data on recurrences, bleeding complications and follow-up. The large percentage of time that the patients spent in the therapeutic range of anticoagulation confirms the high quality of care they received. Moreover, we report previously undescribed outcomes in daily clinical practice of a unique treatment recommendation for patients with a second VTE. Finally, the recurrence risk in the group treated indefinitely as well as the observation that patients most frequently develop a recurrence of the same type, either DVT or PE, are in accordance with findings in previous large studies and therefore indicate that we studied a representative cohort of patients [16].

Our analyses have limitations, of which the most important are related to the observational design of the study. As a result, the choice of patients who received treatment of a limited duration was not randomized, which may have resulted in a selection bias. As argued before, it is more likely that this would have resulted in an underestimation of the recurrence risk after a limited duration of treatment than in an overestimation. It is, therefore, very unlikely that our conclusions would have been different had a different study design been used. Also inherent to the design, is that 40% of the patients were treated for less than 12 months, despite the recommendation of a treatment duration of 12 months in the Dutch multidisciplinary guidelines. We did not, however, find a higher recurrence risk in patients treated for 3 or 6 months compared to that in patients treated for 12 months suggesting that this factor was of no or only little influence on our results. In addition, in a meta-analysis by Van Dongen and colleagues it was demonstrated that the recurrence risk after VTE did not depend on the duration of treatment, although this concerned a study of patients with a first VTE [4]. The lack of long-term follow-up data of the larger population from which our study subjects were derived, i.e. all patients with a diagnosis of first or recurrent VTE, did not allow us to compare the recurrence rate after a

second VTE to that after a first VTE. Finally, due to the relatively small number of patients the confidence intervals for our primary and secondary endpoints were wide, especially for the subgroup analyses.

In conclusion, our study provides insight into the risk of recurrence after treatment of limited duration for a late second VTE, which exceeded the risk of hemorrhage associated with extended anticoagulant treatment in our cohort. We, therefore, argue that most patients with a late second VTE are generally better served by treatment of indefinite duration, although the risk-benefit ratio of extended anticoagulant treatment should be weighed for every individual patient in daily clinical practice.

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CHAPTER 9

Cohort study on the management of cancer-associated venous thromboembolism aimed at the safety of stopping anticoagulant therapy in patients cured of cancer

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ABSTRACT

Background

After diagnosis of cancer-associated venous thromboembolism (VTE), guidelines recommend considering the continuation of anticoagulant treatment until the patient is cured of cancer, although the safety of stopping anticoagulant treatment after the patient is cured has never been evaluated.

Methods

We conducted a cohort study in consecutive patients in whom cancer-associated VTE was diagnosed at the Leiden University Medical Center between January 2001 and January 2010 and monitored for the effect of cancer treatment, occurrence of recurrent VTE, major hemorrhage, and death.

Results

Of the 358 patients with cancer-associated VTE, anticoagulant treatment was continued until the death of 207 patients. In another 12 patients anticoagulant treatment was continued because of an alternative indication despite their being cured of cancer. Anticoagulant treatment was stopped in 50 patients for reasons other than major hemorrhage despite active cancer, in 21 patients after major hemorrhage, and in 68 patients after they had been cured of cancer. Among these 68 patients, 10 patients received a diagnosis of symptomatic recurrent VTE during a cumulative follow-up of 311 years, resulting in an incidence rate of 3.2 per 100 patient-years (95% CI, 1.5-5.9). Seven of these 10 patients with recurrent VTE experienced a cancer relapse during follow-up. For the 50 patients who stopped anticoagulant treatment despite active cancer the recurrent VTE incidence rate was 19 per 100 patient-years (11 events during 59 years of follow-up; 95% CI, 9.3-33).

Conclusions

Our data support the recommendation to stop anticoagulant treatment of cancer-associated VTE in patients cured of cancer. A cancer relapse seems to be a strong risk factor for recurrent symptomatic VTE.

INTRODUCTION

Venous thromboembolism (VTE) is a well-recognized complication in the course of cancer and causes significant morbidity and mortality. Arterial and venous thromboembolism has been reported to be the second leading cause of death among patients with cancer, after cancer itself [1]. Also, all-cause mortality is higher in patients with cancer-associated VTE compared with matched patients with cancer but without concomitant VTE [2]. Established risk factors for cancer-associated VTE include metastatic disease, the presence of central venous catheters, chemotherapy, recent surgery, and immobilization [3-4].

Treatment of cancer-associated VTE is challenging because of the high risk of both recurrent VTE and major hemorrhage under anticoagulant treatment, with hazard ratios of 3.2 (95% confidence interval [CI], 1.9-5.4) and 2.2 (95% CI, 1.2-4.1), respectively, compared with patients with VTE but without cancer. The 12-month cumulative risk of recurrent VTE and major hemorrhage in patients with cancer while receiving anticoagulant treatment has been reported to be as high as 21% and 12%, respectively, compared with 6.8% and 4.9% in patients without cancer [5]. Both the type of anticoagulant treatment and the optimal duration of treatment have been debated [6-9]. In the absence of evidence from clinical trials, treatment of cancer-associated VTE beyond the initial 6 months after diagnosis remains controversial. Since the risk of recurrent VTE after the initial 6 months is believed to remain high, some authors have considered continuing anticoagulant treatment as long as the cancer is active [7-8,10-11]. The American Society of Clinical Oncology guideline recommends considering continuation of anticoagulant treatment only for selected patients with active cancer, such as patients with metastatic disease or those receiving chemotherapy [11]. On the other hand, some patients with cancer-associated VTE successfully complete a curative anticancer treatment, for instance, radical surgery or adjuvant chemotherapy, and in these patients the VTE recurrence risk is assumed to be low since the provoking factor is no longer present. Consequently, in these patients who are cured of cancer anticoagulant treatment could possibly be stopped, although the safety of treatment withdrawal has never been investigated [7-8,10]. Therefore, we evaluated the treatment of cancer-associated VTE in daily clinical practice, with the aim of determining the safety of stopping anticoagulant therapy in patients cured of cancer.

MATERIALS AND METHODS

Patients

This was an observational chart review study including all consecutive patients in whom cancer-associated VTE was diagnosed in the period from January 2001 to January 2010 at the Leiden University Medical Center (Leiden, the Netherlands). VTE was defined as a diagnosis of either pulmonary embolism (PE), lower extremity deep vein thrombosis (DVT), or upper extremity DVT. PE had to be confirmed by contrast-enhanced CT scan or by ventilation-perfusion (V/Q) lung scan, and DVT had to be confirmed by (compression) ultrasonography or CT venography in accordance with current guidelines [7,12]. Patients with symptomatic VTE as well as those with incidentally diagnosed VTE were included in this study. Active cancer was defined as cancer diagnosed within 6 months of the diagnosis of VTE (excluding basal cell or squamous cell carcinoma of the skin), recently recurrent or progressive cancer, or any cancer that required anticancer treatment within the 6 months preceding the diagnosis of VTE. Patients with solid malignancies as well as those with hematologic malignancies were eligible.

Patients with cancer-associated VTE were treated according to local clinical practice. Before 2007, standard treatment of cancer-associated VTE was initially low-molecular-weight heparin (LMWH) or unfractionated heparin followed by long-term vitamin K antagonists (VKA). From 2007, standard treatment consisted of weight-adjusted therapeutic nadroparin (171 International Units of anti-factor Xa/kg once daily). The initial duration of treatment of cancer-associated VTE was 3 to 6 months. Thereafter an indefinite duration of treatment was considered for all patients with active cancer, although the guideline allowed physicians to consider a limited duration of treatment after weighing the risk of recurrent VTE and the risk of major hemorrhage. For patients with an upper extremity DVT associated with a central venous catheter that was removed, the standard duration of treatment was 4 weeks after removal of the central venous catheter. Incidentally diagnosed and symptomatic VTE were treated in the same way [7-8,10]. The institutional review board of the Leiden University Medical Center approved the study and waived the need for informed consent.

Study Aims, End Points, and Follow-up Procedures

The primary aim of this study was to determine the incidence rates of recurrent VTE and major hemorrhage after stopping anticoagulant treatment in patients who were considered to be cured of cancer. The secondary aims were (1) to evaluate the clinical course if a cancer relapse or new cancer was diagnosed, (2) to determine the incidence rates of recurrent VTE and major hemorrhage after anticoagulant treatment was stopped for reasons other than major hemorrhage in patients with active cancer, and

(3) to determine the incidence rates of recurrent VTE and major hemorrhage in patients while receiving anticoagulant treatment.

Recurrent PE was defined as a new intraluminal filling defect on pulmonary angiography or computed tomographic pulmonary angiography, a new high-probability perfusion defect on V/Q scan or any new defects after earlier normalization of the scan, or confirmation of a new PE at autopsy. V/Q scans were evaluated according to PIOPED (Prospective Investigation of Pulmonary Embolism Diagnosis) criteria. Recurrent lower extremity DVT was defined as new noncompressibility by ultrasonography of the common femoral and/or popliteal vein in the transverse plane or as an increase in vein diameter under maximal compression, as measured in the abnormal venous segment, indicating an increase in thrombus diameter (≥ 4 mm). Recurrent upper extremity DVT was defined as evidence of VTE in the subclavian, axillary, and/or brachial vein on ultrasonography or CT venography [12]. Incidentally diagnosed VTEs detected on imaging for oncologic staging were not counted toward the end points in this study, since it is highly complicated to decide whether signs of VTE on a nondedicated imaging test after the initial VTE represent recurrent or residual VTE.

Secondary end points included fatal PE, major hemorrhage, fatal hemorrhage, a cancer relapse, a new diagnosis of cancer, and death. Major hemorrhage was defined in accordance with the International Society on Thrombosis and Haemostasis criteria [13]. The cause of death was verified by reviewing medical records and, if available, the pathology.

All patients were monitored regularly in the context of standard clinical care by their oncologist for new signs or symptoms of a malignancy according to relevant oncology guidelines, as well as the occurrence of symptomatic recurrent VTE. Patients were monitored until their last visit to our hospital, until death, or until September 2014. Medical records were reviewed by two reviewers for the occurrence of end points of the study (T. v. d. H. and P. v. d. H.).

Patients were considered to be cured of cancer or "in complete remission" when the following criteria were fulfilled: (1) there were no signs and symptoms suggestive of residual or recurrent disease; (2) anticancer treatment with a curative intent had been completed, including adjuvant hormonal therapy and chemotherapy; (3) a reasonable chance of cure existed, taking into account the cancer type and stage (ie, nonmetastatic disease or an objectively determined response to treatment). The final decision as to whether a patient was considered to be cured was made by the treating oncologist. A new diagnosis or a recurrence of cancer had to be confirmed by tissue sampling.

Analyses and Statistics

To provide an overview of the total cohort, 6- and 12-month cumulative incidence rates of recurrent VTE, major hemorrhage while receiving anticoagulant treatment, and death

were calculated according to the Kaplan-Meier method, starting at the time of diagnosis of cancer-associated VTE.

For analysis of the primary and secondary end points, follow-up started at the time anticoagulant treatment was stopped and censored at the time of a recurrent VTE, major hemorrhage, death, or last follow-up, whichever came first. Incidence rates were calculated according to the Kaplan-Meier method with 95% CI. No direct comparisons between patient groups were performed.

All analyses were repeated after excluding patients with an incidentally diagnosed VTE. Data were analyzed with SPSS version 20 (SPSS Inc).

RESULTS

Three hundred and fifty-eight patients received a diagnosis of cancer-associated VTE (**Table 1**). The mean age was 59 years (SD, 15), 189 patients (53%) were male, and 282 patients (79%) had metastatic cancer. Two hundred and thirty-one patients (65%) had PE (with or without DVT), 96 patients (27%) had an isolated DVT of the lower extremities, and 31 patients (8.7%) had an isolated DVT of the upper extremities. VTE was incidentally diagnosed in 61 patients (17%), of whom 55 patients had PE, five patients had lower extremity DVT, and one patient had upper extremity DVT. Only in 17 of the 231 patients (7.4%) with PE was the diagnosis based on a V/Q scan; of these, two patients also received a diagnosis of DVT. In the remaining 214 patients with PE the diagnosis was based on CT scan. Of the 358 patients, 142 patients (40%) were treated with long-term LMWH, 205 patients (47%) with VKA, nine patients (2.5%) were treated with intravenous unfractionated heparin, one patient (0.3%) was in a terminal phase of cancer and anticoagulant treatment was withheld, and one patient (0.3%) was treated with an inferior vena cava filter only because of concurrent major hemorrhage. For the total cohort, the 6- and 12-month cumulative mortality risks were 45% (SE, 0.026) and 57% (SE, 0.026), respectively. Of the 204 patients who died within the first 12 months of follow-up, the cause of death was directly related to the cancer in 167 patients (82%). Six patients (2.9%) had a fatal hemorrhage; seven patients (3.4%) had a (high suspicion of) fatal PE; 20 patients (9.8%) died of another, directly related cause; and in four patients (2.0%) the cause of death was unclear. Thirty-three recurrent VTE events occurred among patients while receiving anticoagulant treatment during a cumulative follow-up of 282 years, for an incidence rate of 12 per 100 patient-years (PY) (95% CI, 8.1-16). Major hemorrhage occurred in 53 patients while receiving anticoagulant treatment during a cumulative follow-up of 240 years, for an incidence rate of 22 per 100 PY (95% CI, 17-29). Outcomes while receiving anticoagulant treatment were comparable between patients with inci-

Table 1. Patient characteristics.

Characteristic	Total cohort n=358	AC stopped after cure from cancer n=68	AC stopped for reasons other than major haemorrhage despite active cancer n=50
Mean age (SD)	59 (15)	53 (17)	56 (15)
Male sex, n (%)	189 (53)	35 (51)	27 (54)
Previous VTE, n (%)	30 (8.4)	3 (4)	6 (12)
Metastatic cancer, n (%)	282 (79)	38 (56)	43 (86)
Surgery < 4 weeks, n (%)	64 (18)	25 (37)	5 (10)
Immobilization <4 weeks, n (%)	157 (44)	44 (65)	20 (40)
Incidentally diagnosed, n (%)	61 (17)	14 (21)	6 (12)
Cancer type, n (%)			
Lung	54 (15)	2 (3)	4 (8)
Colorectal	24 (7)	3 (4)	3 (6)
Other gastrointestinal	42 (12)	10 (15)	2 (4)
Breast	28 (8)	0 (0)	7 (14)
Testicular	15 (4)	11 (16)	2 (4)
Gynaecological	22 (6)	6 (9)	5 (10)
Central nervous system	10 (3)	0 (0)	1 (2)
Other solid	98 (27)	17 (25)	9 (18)
Multiple Myeloma	10 (3)	2 (3)	6 (12)
Non-Hodgkin lymphoma	22 (6)	7 (10)	5 (10)
Other haematological	33 (9)	10 (15)	6 (12)
Type of VTE, n (%)			
PE (±DVT)	231 (65)	48 (71)	31 (62)
Lower extremity DVT	96 (27)	15 (22)	14 (28)
Upper extremity DVT	31 (9)	5 (7)	5 (10)
Treatment, n (%)			
LMWH	142 (40)	30 (44)	11 (22)
VKA	205 (57)	38 (56)	39 (78)
Other/none	11 (3)	0 (0)	0 (0)

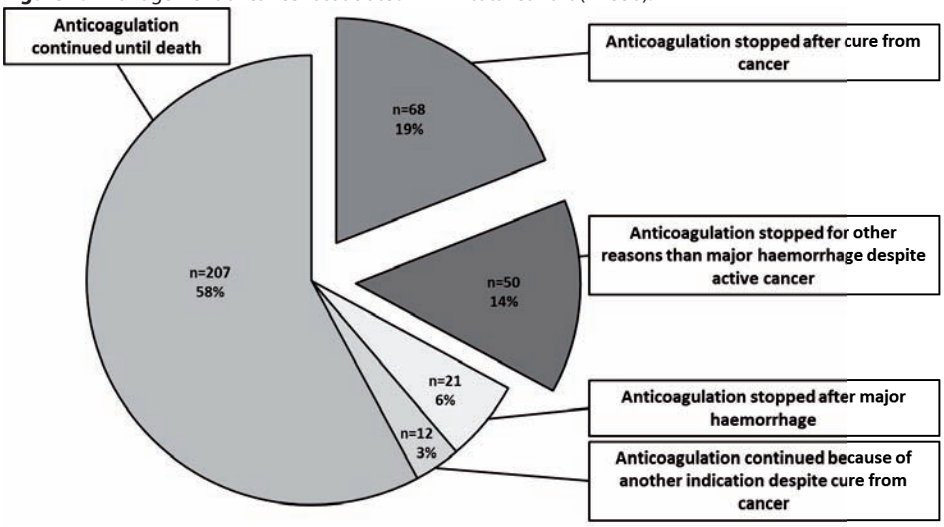
Note: AC: anticoagulation; SD: standard deviation; VTE: venous thromboembolism; PE: pulmonary embolism; DVT: deep vein thrombosis; LMWH: low-molecular-weight-heparin; VKA: vitamin K antagonists.

dental VTE and those with symptomatic VTE, and in the period 2001-2005 compared with 2006-2010 (data not shown).

Patients Cured of Cancer

Of the 358 patients, 80 patients (22%) were cured of cancer during follow-up, of whom 12 patients had another indication for continuing anticoagulant treatment: eight patients received a diagnosis of atrial fibrillation, two had a persistent vena cava inferior filter, one patient had a history of recurrent VTE, and one patient was immobilized (**Figure 1**). In the remaining 68 patients, whose baseline characteristics are shown in **Table 1**, anticoagulant treatment was stopped after a median duration of 6.0 months (interquartile range, 4.7-6.7 months).

Figure 1. Management of cancer-associated VTE in total cohort (n=358).



After anticoagulant treatment had been stopped, 10 patients had a symptomatic recurrent VTE during a cumulative follow-up of 311 years, for an incidence rate of 3.2 per 100 PY (95% CI, 1.5-5.9) (**Figure 2, Table 2**). Three of these patients had PE, five patients had a lower extremity DVT, and two patients had an upper extremity DVT. No incidental VTEs were diagnosed among these patients. In 15 of the 68 patients (22%) a cancer relapse was diagnosed, and three patients (4.4%) received a diagnosis of a new primary malignant tumor. Of the 10 recurrent VTE events, seven events occurred in patients who also experienced a cancer relapse: five occurred in patients who shortly before or at the same time received a diagnosis of a cancer relapse, two patients experienced a cancer relapse 9 and 14 months after the recurrent VTE event, and three patients remained free of a cancer relapse. Seven of the 15 patients (47%) with a cancer relapse also experienced a recurrent VTE. A major hemorrhage occurred in four of the 68 patients after anticoagulant treatment was stopped during a cumulative follow-up of 303 years, resulting

in an incidence rate of 1.3 per 100 PY (95% CI, 0.4-3.4). None of the major hemorrhages occurred in patients in whom a cancer relapse or new cancer was diagnosed.

Patients Not Cured of Cancer in Whom Anticoagulant Treatment Was Stopped

In 50 of the 278 patients with active cancer, anticoagulant treatment was stopped for reasons other than the occurrence of a major hemorrhage after a median duration of 5.8 months (interquartile range, 3.9-6.5 months). In nine of these 50 patients a reason for stopping anticoagulant treatment was documented, that is, a supposed high risk of major hemorrhage or frequently planned invasive procedures. In the remaining 41 patients a limited duration of treatment was considered to be sufficient, although it cannot be completely excluded that this decision was influenced by the presence of any relative contraindication, for instance, an estimated higher-than-standard risk of major hemorrhage. After anticoagulant treatment was stopped, a nonfatal recurrent VTE developed in 11 patients during a cumulative follow-up of 59 years, resulting in an incidence rate of 19 per 100 PY (95% CI, 9.3-33) (**Figure 2, Table 2**). A major hemorrhage occurred in three patients after anticoagulant treatment was stopped during a cumulative follow-up of 59 years, for an incidence rate of 5.1 per 100 PY (95% CI, 1.1-15).

Table 2. Risk of recurrent VTE and major haemorrhage.

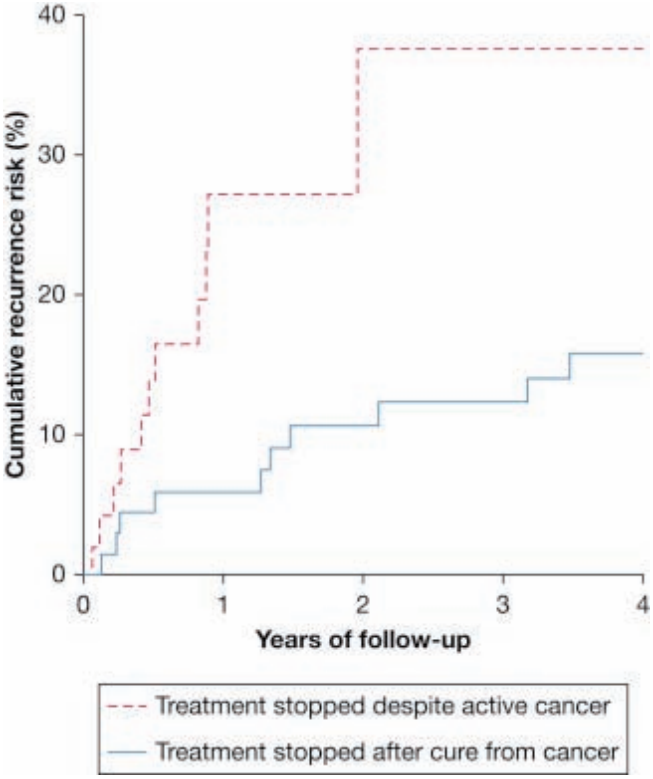
	Events / cumulative follow-up Incidence rate (95% CI)	
Category	**Recurrent VTE**	**Major haemorrhage**
While on anticoagulant treatment for total cohort	33 / 282 years 12 / 100 PY (8.1-16)	53 / 240 years 22 / 100 PY (17-29)
Anticoagulant treatment stopped after cure from cancer	10 / 311 years 3.2 / 100 PY (1.5-5.9)	4 / 303 years 1.3 / 100 PY (0.4-3.4)
Anticoagulant treatment stopped for reasons other than major haemorrhage despite active cancer	11 / 59 years 19 / 100 PY (9.3-33)	3 / 59 years 5.1 / 100 PY (1.1-15)

Note: VTE: venous thromboembolism; CI: confidence interval; PY: patient years.

DISCUSSION

The key finding of our study is the 3.2-per-100 PY (95% CI, 1.5-5.9) incidence rate of recurrent VTE in patients whose anticoagulant treatment was stopped after they were cured of cancer. This rate is fully comparable to the VTE recurrence rate of 3.3 per 100 PY (95% CI, 2.8-3.9) after stopping anticoagulant treatment in patients with a first VTE related to a transient provoking factor, in whom a 3- to 6-month duration of anticoagulant

Figure 2. Cumulative incidence rate of recurrent VTE and major haemorrhage in patients who stopped anticoagulation after cure from cancer (straight line) and after stopping anticoagulation for other reasons than major haemorrhage despite active cancer (dotted line).



treatment is generally accepted [7-8,14]. Also, the incidence rate of recurrent VTE after stopping anticoagulant treatment can be weighed relative to the risk of major hemorrhage associated with long-term anticoagulant treatment, which has been estimated to be 2.74 per 100 PY (95% CI, 2.71-2.77) [15]. Since the case fatality rate for a major hemorrhage has been reported to be higher than that for a recurrent VTE, one ought to consider the clinical impact of major hemorrhage to be at least comparable to that of recurrent VTE. On the basis of both comparisons, we conclude that stopping anticoagulant treatment of cancer-associated VTE in patients who are cured of cancer is justified. Although this is in accordance with current guidelines, this is to our knowledge the first study supporting this recommendation [7-8].

A second important observation from our study is the association between cancer relapse and the risk of recurrent VTE: 47% of the patients with a prior cancer-associated VTE event who experienced a cancer relapse were diagnosed with recurrent VTE. From another point of view, 70% of recurrent VTE events occurred among the patients with a cancer relapse. Given these results, although based on small numbers of patients,

the question arises whether patients with cancer and previous cancer-associated VTE are candidates for ambulatory pharmacologic VTE prophylaxis. Until now, it has been proven difficult to identify patients with cancer who would benefit from thromboprophylaxis [16-17]. The Khorana prediction score has been developed for this purpose, and in a validation cohort with an overall PE incidence of 2.1% during 2.5 months of follow-up this score was successfully used to differentiate between patients with low, intermediate, and high risk of VTE (0.3%, 2.0%, and 6.7%, respectively) [18]. Whether the Khorana score is sufficient to identify patients at such a high risk that VTE prophylaxis is justified remains to be determined in a management study. Interestingly, this score does not award points for a history of VTE since this information was unavailable in the derivation cohort. Therefore, it seems relevant to investigate whether a history of (cancer-associated) VTE should be incorporated in prediction scores in future outcome studies.

Our study provides further insight in the long-term treatment of cancer-associated VTE in patients with persistently active cancer. The 19 per 100 PY incidence rate of recurrent VTE in patients in whom anticoagulant treatment was stopped for reasons other than major hemorrhage confirms the persistently high risk of recurrent VTE beyond the initial 6-month period. It should be emphasized that in some of these patients anticoagulant treatment was stopped, based on an assessment of the risk-to-benefit ratio of continued anticoagulant treatment. This finding should, therefore, be interpreted cautiously.

The observational study design in a single academic hospital is the most important limitation of our study. As a result, the number of included patients cured of cancer was limited, our population may differ somewhat from those in other hospitals, and outcomes may not have been noted in the medical records and therefore missed in this study. Also, recommendations regarding the treatment of cancer-associated VTE changed during the study period, with LMWH replacing VKA as the treatment of choice being the most notable difference. However, the primary outcome of this study was to determine the risk of recurrent VTE after stopping anticoagulant treatment, which is unlikely be influenced by the type of initial treatment. The major strength of this study is the description of all patients with cancer-associated VTE, which enables the assessment of the external validity. The overall survival as well as the outcomes of patients while receiving anticoagulant treatment are in line with results from other studies on cancer-associated VTE [5,19-20].

In conclusion, the VTE recurrence rate after stopping anticoagulant treatment of a cancer-provoked VTE in patients cured of cancer is low, which justifies stopping anticoagulant treatment in these patients. A cancer relapse in the further clinical course is a strong risk factor for recurrent VTE. Whether patients with cancer and a history of (cancer-associated) VTE warrant secondary pharmacologic VTE prophylaxis should be the focus of future studies.

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CHAPTER 10

Meta-analysis of the efficacy and safety of new oral anticoagulants in patients with cancer-associated acute venous thromboembolism

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ABSTRACT

Introduction

Treatment of acute venous thromboembolism (VTE) in cancer patients is challenging, owing to a high risk of recurrent VTE and bleeding complications. The anticoagulants of choice are low molecular weight heparins (LMWH), because of a proven higher efficacy than vitamin K antagonists (VKA) and a similar bleeding profile. The recently introduced new oral anticoagulants (NOAC) have the potential to be alternative options for these patients, as these drugs share practical advantages with LMWH, are administered orally, and had similar efficacy to VKA but a lower bleeding risk in phase 3 studies in the general VTE population.

Methods

A systematic literature search was performed to identify phase 3 trials investigating NOAC for the treatment of VTE. The efficacy outcome was recurrent VTE, and the safety outcome was major and clinically relevant non-major bleeding. Pooled incidence rates and risk ratios (RR) were calculated for cancer patients and non-cancer patients separately.

Results and discussion

Five studies were included, with 19 060 patients, of whom 973 (5.1%) had active cancer. The pooled incidence rates of recurrent VTE were 4.1% (95% confidence interval [CI] 2.6–6.0) in cancer patients treated with NOAC, and 6.1%(95% CI 4.1–8.5) in patients treated with VKA (RR 0.66,95% CI 0.38–1.2). The pooled incidence rates of major or non-major clinically relevant bleeding were 15%(95% CI 12–18) in cancer patients treated with NOAC, and 16% (95% CI 9.9–22) in patients treated with VKA (RR 0.94, 95% CI 0.70–1.3). These results form a solid basis for the initiation of a head-to-head comparison of NOAC with LMWH in cancer patients.

INTRODUCTION

Symptomatic acute venous thromboembolism (VTE) is a common complication in cancer patients, occurring in up to 15% of cancer patients during the course of their disease, and it is the second leading cause of death after the malignancy itself [1,2]. Anticoagulant treatment for acute VTE in cancer patients is complicated by both high risks of recurrent VTE and bleeding complications [3]. Hence, alternative treatment modalities are particularly interesting for this patient category.

In recent years, new oral anticoagulants (NOAC) have been developed, including direct factor IIa inhibitors (i.e. dabigatran) and direct FXa inhibitors (i.e. apixaban, edoxaban, and rivaroxaban), for which similar efficacy to that of vitamin K antagonists (VKA) and a superior safety profile have been reported for the treatment of patients with acute VTE [4–9]. A recent meta-analysis of phase 3 randomized controlled trials (RCT) comparing NOAC with VKA for the initial treatment of acute VTE demonstrated that the incidence of major bleeding (pooled risk ratio [RR] 0.60, 95% confidence interval [CI] 0.41–0.88) and of the combined endpoint of major bleeding and clinically relevant non-major bleeding (pooled RR 0.76, 95% CI 0.58–0.99) were significantly lower for patients treated with one of the NOACs, whereas the risk of recurrent VTE was similar (pooled RR 0.88, 95% CI 0.74 –1.1) [10].

The efficacy and safety of NOAC in patients with cancer-associated VTE have not been specifically addressed so far, although these drugs would constitute an interesting option for this specific patient group, for several reasons. First, the improved safety profile of NOAC may be of particular relevance, owing to the higher anticoagulation-associated bleeding risk observed in cancer patients [3]. This is made even more relevant by the fact that current guidelines recommend continuation of anticoagulant therapy for as long as the cancer is active and the bleeding risk remains acceptable. As a result, patients are exposed to a high risk of bleeding complications for periods ranging from 6 months to many years [11,12]. Second, low molecular weight heparins (LMWH) are the current preferred anticoagulants for cancer-associated VTE, because of their superior efficacy in preventing VTE recurrences, and a similar bleeding profile to that associated with VKA. However, these drugs confront patients with the burden of daily subcutaneous administration [13,14]. For some patients, this may be the reason for asking for VKA. Hence, if shown to be equally effective and safe or even safer, NOAC would have clear advantages over LMWH. Undoubtedly, clinicians will be faced with the choice of whether to use NOAC in cancer patients in the near future. In order to address the lack of any data on the efficacy and safety of NOAC for cancer-associated VTE, we performed a systematic review of the literature, and pooled relevant data in a meta-analysis.

METHODS

We systematically searched MEDLINE (via PubMed), EMBASE, the Cochrane Database of Systematic Reviews and the clinical trials registry from inception to May 2014 to identify randomized controlled trials comparing a NOAC with a VKA or a LMWH in patients with acute VTE, using a similar approach as in a recent meta-analysis [10]. From all identified studies, we included only those in whom outcomes for patients with active cancer were reported separately in the original publication, supplementary information, or related publications. In all included studies, the analysis specifically for cancer patients was a predefined subgroup analysis. If separate results for cancer patients were not available, we requested the pharmaceutical companies for additional information. The primary efficacy outcome of the current study was recurrent VTE, and the safety outcome was major bleeding or clinically relevant non-major bleeding while patients were receiving anticoagulant treatment. Two independent researchers performed the study selection and data abstraction. The quality of the studies was assessed with the Cochrane Collaboration's tool for assessing risk of bias in randomized trials [15]. The only potential risk of bias identified was the open label design with blinded endpoint evaluation of the Einstein studies [10]. Incidence rates were pooled by the use of DerSimonian-Laird weights for the random effects model. RR with concomitant 95% CI were calculated with the Mantel–Haenszel random effects model, through REVIEW MANAGER (V. 5.1; The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark). Assessment of heterogeneity was performed by calculation of the I^2 statistic.

RESULTS AND DISCUSSION

We identified six potentially relevant studies [4-9], all comparing NOAC with VKA. Separate outcomes for patients with active cancer were reported for all studies except for the Amplify study, in which apixaban was investigated [9]. We asked the manufacturer for additional information, but this was not provided (the search strategy and flow chart are provided in Data S1 and Data S2 available at http://onlinelibrary.wiley.com/journal/10.1111/(ISSN)1538-7836/). For the Re-Cover I and II studies, safety outcomes for cancer patients were only mentioned separately in an abstract presented at the Annual Meeting of the American Society of Hematology in 2013 [16]. Hence, we were able to include five studies, among which the results of the Re-Cover I and II studies are presented in combination.

The characteristics of the included RCT have been described in detail previously [4–10]. All studies compared a NOAC at a standard dosage with VKA treatment with a target International Normalized Ratio between 2.0 and 3.0. In total, the studies included 19 060

patients, of whom 973 (5.1%) had active cancer. Across the individual studies, the percentage of patients with an active malignancy ranged from 2.5% to 6.6%. Of the patients with active cancer, 514 (53%) were treated with a NOAC and 459 (47%) with a VKA.

The incidence rates of recurrent VTE in cancer patients treated with a NOAC varied from 1.8% to 5.8%, and those in cancer patients treated with a VKA varied from2.8% to 7.4% (**Table 1**). The pooled incidence rates were 4.1% (95% CI 2.6–6.0) for NOAC and 6.1% (95% CI 4.1–8.5) for VKA, with a non-significant pooled RR of 0.66 (95% CI 0.38–1.2) in favor of NOAC (**Figure 1**). For patients without active cancer, the recurrent VTE incidence rate varied from 2.0% to 3.0% in patients treated with NOAC, and from 1.8% to 3.5% in patients treated with VKA. The pooled incidence rates were 2.6% (95% CI 2.3–2.9) and 2.5% (95% CI 1.8–3.4) for NOAC and VKA, respectively, with a pooled RR of 0.98 (95% CI 0.83–1.2).

Table 1. The risk of recurrent venous thromboembolism and major bleeding in cancer patients and non-cancer patients separately.

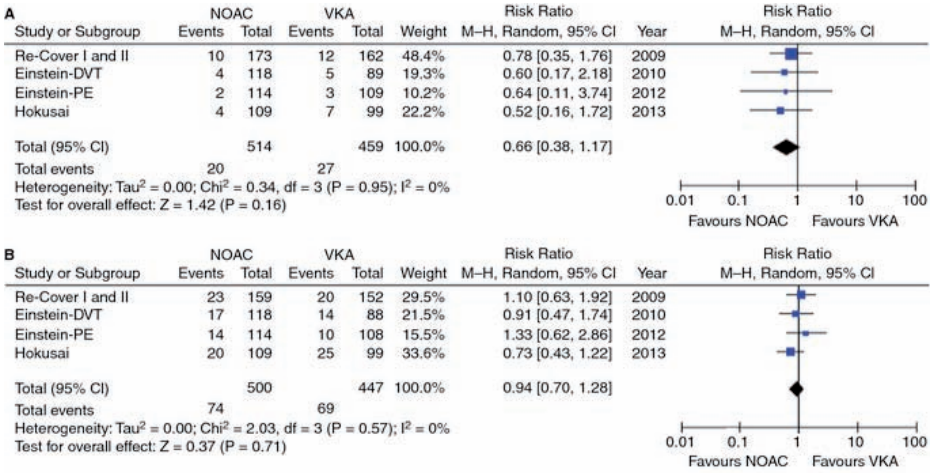
Study drug	Active cancer (%)	Recurrent VTE		Major bleeding and clinically relevant non-major bleeding	
		NOAC, no. (%)	VKA, no. (%)	NOAC, no. (%)	VKA, no. (%)
Dabigatran, Re-Cover I and II [16]	No (93.4)	58/2380 (2.4)	50/2392 (2.1)	86/2297 (3.7)	169/2310 (7.3)
	Yes (6.6)	10/173 (5.8)	12/162 (7.4)	23/159 (14.5)	20/152 (13.2)
Rivaroxaban, Einstein-DVT [6]	No (94.0)	32/1613 (2.0)	46/1629 (2.8)	122/1600 (7.6)	124/1623 (7.6)
	Yes (6.0)	4/118 (3.4)	5/89 (5.6)	17/118 (14.4)	14/88 (15.9)
Rivaroxaban, Einstein-PE [7]	No (95.4)	48/2305 (2.1)	41/2304 (1.8)	235/2298 (10.2)	264/2297 (11.5)
	Yes (4.6)	2/114 (1.8)	3/109 (2.8)	14/114 (12.3)	10/108 (9.3)
Edoxaban, Hokusai-VTE [8]	No (97.5)	126/4009 (3.1)	139/4023 (3.5)	329/3740 (8.1)	398/4023 (9.9)
	Yes (2.5)	4/109 (3.7)	7/99 (7.1)	20/109 (18.3)	25/99 (25.3)

Note: NOAC, new oral anticoagulant; VKA, vitamin K antagonist.

The incidence rate of the combined endpoint of major bleeding and clinically relevant non-major bleeding varied from 12% to 18% in cancer patients treated with NOAC, and from 9.9% to 25% in cancer patients treated with VKA. Pooled incidence rates were 15% (95% CI 12–18) and 16% (95% CI 9.9–22), respectively, and the corresponding RR was 0.94 (95% CI 0.70–1.3) (**Figure 1**). In non-cancer patients, the incidence rate of major bleeding and clinically relevant non-major bleeding varied from 3.7% to 10% in patients treated with NOAC, and from 7.3% to 11% in patients treated with VKA. Pooled incidence rates were 7.4% (95% CI 4.8–11) and 9.1% (95% CI 7.3–11), with an RR of 0.81% (95% CI 0.64–1.02) in favor of NOAC. The I^2 of all evaluated efficacy and safety outcomes was 0%, indicating low heterogeneity.

In summary, the most important results of this study are the RR of 0.66 (95% CI 0.38–1.2) for recurrent VTE and 0.94 (95% CI 0.70–1.3) for major bleeding and clinically relevant

Figure 1. Meta-analysis.
Risk ratios of recurrent venous thromboembolism (A) and major bleeding and clinically relevant non-major bleeding (B) in cancer patients with acute VTE.



Note: CI, confidence interval; d.f., degrees of freedom; M–H, Mantel–Haenszel; NOAC, New oral anticoagulant; VKA, vitamin K antagonist.

non-major bleeding, indicating that both the efficacy and safety of NOAC in cancer patients were at least comparable to those of VKA. These results require comment, and some of them should be interpreted with caution. First, none of the included studies gave a detailed definition of 'active cancer'. Only in the abstract of the Re-Cover studies was a definition given: 'a diagnosis of cancer (other than basal-cell or squamous-cell carcinoma of the skin) within 5 years before enrolment; any treatment for cancer within 5 years before enrolment; or recurrent or metastatic cancer'; the more generally used standard definition is 'a diagnosis of cancer within 6 months prior to enrolment, any treatment for cancer within the previous 6 months, or recurrent or metastatic cancer' [13,14]. This specific definition and the use of certain exclusion criteria in the trials (e.g. 'a limited life-expectancy' and 'a high bleeding risk') suggest that the cancer patients in the studies were relatively healthy, and do not compare well with those in previous trials, which were specifically designed for patients with acute VTE and active cancer [17]. This is further emphasized by the observed VTE recurrence risk of 6.1% in cancer patients treated with VKA in the NOAC studies, which is considerably lower than the 16% and 17% reported in two previous studies specifically performed in a population with active cancer [13,14].

Second, NOAC were compared only with VKA in the available studies, whereas LMWH constitute the current treatment of choice for cancer-associated acute VTE [11,12]. Hence, NOAC should preferably be compared with LMWH to investigate their efficacy and safety in patients with cancer-associated VTE. In a Cochrane meta-analysis, it was

demonstrated that LMWH have a similar safety profile to VKA (RR for major bleeding of 1.05, 95% CI 0.53–2.1), with higher efficacy in preventing recurrent VTE (RR 0.47, 95% CI 0.32–0.71) [17]. Interestingly, and supportive for future trials, the RR for NOAC as compared with VKA in our meta-analysis show the same trend. A lack of power (973 patients in our meta-analysis vs. 1325 patients in the Cochrane meta-analysis) might be the cause of statistical significance not being reached for the efficacy outcome.

Third, whereas previous studies have demonstrated non-inferior safety of LMWH as compared with VKA with regard to the risk of major bleeding, only the numbers for the combined endpoint of major and clinically relevant non-major bleeding were available for NOAC. Major bleeds in cancer patients were not separately reported. Also, the number of VTE recurrences in the studies was too low for comparison of the severity of these events, i.e. risk of fatal pulmonary embolism or risk of recurrent deep vein thrombosis versus recurrent acute pulmonary embolism.

Fourth, NOAC share many of the advantages of LMWH over VKA, such as the lack of the need for monitoring of anticoagulant effect and the shorter half-life, which facilitates temporary interruptions for invasive procedures or when thrombocytopenia occurs [18]. On the other hand, the oral administration might raise concerns in cancer patients about gastrointestinal tract absorption during episodes of vomiting or mucositis. A potential additional disadvantage of NOAC is the existence of drug interactions with several chemotherapeutic agents and drugs used for supportive care through the CYP3A4 enzyme and/or P-glycoprotein transporter, although the clinical implications of these interactions are not yet known. However, drug interactions also exist for VKA and several chemotherapeutic agents. Capecitabine, for instance, may enhance the anticoagulant effect of VKA, and thereby increase the risk of major bleeds [19].

A final concern is the current unavailability of specific antidotes for NOAC, which may be problematic in cases of severe life-threatening major bleeding or emergent invasive procedures. It is acknowledged that antidotes are under development, and phase 3 trials with antidotes are currently being planned [20,21].

In conclusion, we have demonstrated that both the efficacy and safety of NOAC in the treatment of cancer-associated acute symptomatic VTE are at least comparable to those of VKA. This suggests that, for cancer patients without major bleeding risks, the use of NOAC is not contraindicated. However, the current NOAC trials in VTE management were clearly not designed to provide definite conclusions on the efficacy and safety of NOAC in cancer patients, relative to LMWH. Because of the lack of a direct comparison with LMWH with selective inclusion of cancer patients only, NOAC cannot yet be recommended as the first-line treatment for VTE in cancer patients. Nonetheless, our results strongly support the initiation of a head-to-head comparison of NOAC with LMWH in the near future.

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CHAPTER 11

Risk of recurrent venous thromboembolism and major hemorrhage in cancer-associated incidental pulmonary embolism among treated and untreated patients: a pooled analysis of 926 patients

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ABSTRACT

Background

Incidental pulmonary embolism (IPE) is defined as pulmonary embolism (PE) diagnosed on computed tomography scanning not performed for suspected PE. IPE has been estimated to occur in 3.1% of all cancer patients and is a growing challenge for clinicians and patients. Nevertheless, knowledge about the treatment and prognosis of cancer-associated IPE is scarce. We aimed to provide the best available evidence on IPE management.

Methods

Incidence rates of symptomatic recurrent venous thromboembolism (VTE), major hemorrhage, and mortality during 6-month follow-up were pooled using individual patient data from studies identified by a systematic literature search. Subgroup analyses based on cancer stage, thrombus localization, and management were performed.

Results

In 926 cancer patients with IPE from 11 cohorts, weighted pooled 6-month risks of recurrent VTE, major hemorrhage and mortality were 5.8% (95% confidence interval [CI] 3.7–8.3%), 4.7% (95% CI 3.0–6.8%), and 37% (95% CI 28–47%). VTE recurrence risk was comparable under low molecular weight heparins (LMWH) and vitamin K antagonists (VKA) (6.2% vs. 6.4%; hazard ratio [HR] 0.9; 95% CI 0.3–3.1), while 12% in untreated patients (HR 2.6; 95% CI 0.91–7.3). Risk of major hemorrhage was higher under VKA than under LMWH (13% vs. 3.9%; HR 3.9; 95% CI 1.6–10). VTE recurrence risk was comparable in patients with a subsegmental IPE and those with a more proximally localized IPE (HR 1.1; 95% CI 0.50–2.4).

Conclusion

These results support the current recommendation to anticoagulate cancer-associated IPE with LMWH and argue against different management of subsegmental IPE.

INTRODUCTION

Incidental pulmonary embolism (IPE) is defined as pulmonary embolism diagnosed on a computed tomography (CT) scan performed for reasons other than a clinical suspicion of pulmonary embolism (PE). In cancer patients, IPE has been estimated to occur in 2.2% to 4.1% [1]. Knowledge of the clinical implications of cancer-associated IPE is scarce and almost entirely based on small observational studies. Key finding of these studies was the similar prognosis with regard to recurrence risk, major hemorrhage, and mortality in cancer patients with IPE compared with those with proven symptomatic PE (SPE) [2-4]. Based on these observations, international guidelines recommend an identical anticoagulant treatment regimen for cancer-associated IPE and SPE, and consequently, almost all patients with IPE receive anticoagulant treatment (ACCP level of Evidence 2B) [5, 6].

However, it should be noted that the supporting evidence for this recommendation is limited by the small size of the studies. In addition, essential clinical questions on the subject of IPE management remain unanswered, namely (i) the risks of recurrent venous thromboembolism (VTE) if left untreated, (ii) the risks of hemorrhage and its dependence on the type of anticoagulation, and (iii) the relevance of subsegmental IPE versus more centrally located IPE. To provide the best available evidence on the management of IPE, we pooled individual patient data from 11 observational studies and ongoing registries, which were identified by a systematic literature search.

METHODS

Data sources, searches, and study selection

We searched PubMed, MEDLINE, EMBASE, Web of Science, Academic Search Premier, Science Direct, and the Cochrane Database of systematic reviews for publications concerning cancer patients with IPE from inception to November 2013. The search strategy is provided in the Supplementary Data (all supplementary data is available at http://onlinelibrary.wiley.com/journal/10.1111/(ISSN)1538-7836/). The electronic search was complemented by a manual review of reference lists of relevant articles, and we contacted experts to ask about the existence of unpublished cohorts.

References were screened for relevance by two independent reviewers based on the title and abstract (T.v.d.H. and P.d.E.). Discrepancies were resolved by consensus after contacting a third reviewer (F.K.). Abstracts or fulltext articles identified by either reviewer as potentially relevant were retrieved for further evaluation. Predefined inclusion criteria for eligible cohorts were: (i) ≥ 20 consecutive patients with IPE; (ii) patients with a concomitant active cancer (both solid and hematologic cancer), defined as cancer diagnosed within 6 months before IPE, recurrence or progressive cancer or any cancer that neces-

sitated curative or palliative treatment within the previous 6 months; (iii) at least 6 months of follow-up; (iv) information about the management of the IPE; and (v) reporting at least one of the predefined primary and/or secondary study end points. Completed studies and ongoing patient registries were eligible. An invitation, and study proposal were sent to the authors of the selected references as well as at least one reminder.

Patients and clinical data collection

IPE was defined as PE detected on a CT scan ordered for reasons other than a clinical suspicion of PE [7]. Patients were managed according to local practices. International guidelines available during the study periods recommended anticoagulant treatment for a period of at least 6 months with prolongation for as long as the cancer was active [5, 8, 9]. Low molecular weight heparin (LMWH) was the treatment of choice for cancer-associated incidental VTE from 2004 on.

Individual patient-level data were collected, consisting of general baseline characteristics, the location of IPE and the applied anticoagulant treatment regimen. The primary end point was the occurrence of symptomatic recurrent VTE, defined as a positive finding of the diagnostic workup of suspected acute PE or DVT of the lower or upper extremities [10]. Incidental VTE events were not adjudicated as recurrent events. Secondary end points included major hemorrhage, fatal hemorrhage, and mortality. The duration of follow-up was 6 months. DVT of the lower extremities was diagnosed in case of non-compressibility by compression ultrasonography at the trifurcation of the popliteal vein or above or, in case of an intraluminal filling defect above the trifurcation of the popliteal vein, by CT or venography [5, 10]. Recurrent PE was diagnosed in case of a new intraluminal filling defect in a subsegmental or larger pulmonary artery, in case of a ventilation/perfusion scanning with a high probability of PE in a new lung segment unaffected by the index IPE, or in case of a new intraluminal filling defect by pulmonary angiography [6]. Major hemorrhage was defined as overt and associated with a decrease in the hemoglobin level of ≥ 2 g/dL, requiring transfusion of ≥ 2 units of blood, occurring in a critical site (intracranial, intraspinal, intraocular, pericardial, intra-articular intramuscular with compartment syndrome, retroperitoneal), or contributing to death [11].

Statistical analysis

The end points were defined and all statistical analyses were performed according to a predefined statistical protocol, agreed on by all authors. Baseline characteristics were reported for the combined cohorts and for subgroups based on the management of the IPE. All outcomes were pooled using the DerSimonian–Laird weights in a random-effects model. Additionally, baseline characteristics and outcomes were reported for the individual cohorts (see supplementary tables available at http://onlinelibrary.wiley.com/journal/10.1111/(ISSN)1538-7836/).

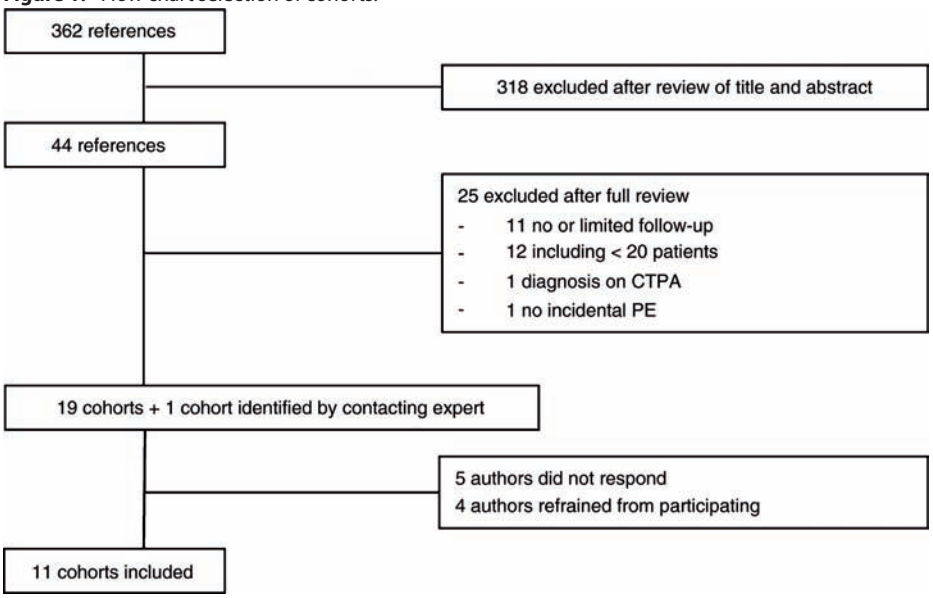
For the subgroup analyses, outcomes were pooled using the DerSimonian–Laird weights in a random effects model. To calculate hazard ratios (HR), all cohorts and registries were combined and considered as one cohort. Subgroups analyses were performed for: (i) patients treated with LMWH, patients treated with vitamin K antagonists (VKA) after an initial course of LMWH, and those who were left untreated; (ii) patients with metastatic cancer and non-metastatic cancer; and (iii) patients with centrally located thrombi (defined as a central or lobar thrombus location) and more peripherally located thrombi (defined as a segmental or subsegmental thrombus location). Additionally, outcomes for patients with isolated subsegmental IPE were reported separately. The HR were calculated using Cox regression analysis. Regarding the subgroup analysis based on management, an intention-to-treat analysis was used for which patients were classified according to the initial management even when anticoagulant treatment was prematurely discontinued. Additionally, per-treatment analysis was performed for which outcomes were related to the management at the time the outcome occurred. A competing risk model was used for the survival tables for recurrent VTE and major bleeding with death as competing risk. spss, version 20 (SPSS Inc, Chicago, IL, USA) and StatsDirect software (StatsDirect Ltd, Cheshire, UK) were used for all analyses.

RESULTS

Identification of cohorts and registries

The initial search identified 106 records in PubMed, 61 unique references in MEDLINE, 153 unique references in EMBASE, 28 unique references in Web of Science, 12 unique references in the Cochrane Database of Systematic Reviews, and two unique references in Academic Search Premier, resulting in a total of 362 references. Based on screening titles and abstracts, 44 references were extensively studied and, when available, read in full text. Of these 44 references, 11 references were excluded because no or only limited follow-up was reported, 12 because they concerned < 20 patients, one because IPE were diagnosed on additionally performed CT pulmonary angiography after the initial CT scan, and one because it did not meet the definition of IPE (see Supplementary Data for excluded references available at http://onlinelibrary.wiley.com/journal/10.1111/(ISSN)1538-7836/). Finally, 19 references from the literature search and one unpublished registry that met our inclusion criteria were included. Patients of the unpublished registry were collected in the Ramón y Cajal Hospital in Madrid, Spain. Of these 20 cohorts, the authors of four references refrained from participating [12-15] and the authors of five references [16-20] did not respond to repeated invitations, resulting in the inclusion of 11 cohorts and registries [2, 4, 21-28] (**Figure 1**).

Figure 1. Flow chart selection of cohorts.



Note: CTPA: Computed tomography pulmonary embolism; PE: Pulmonary embolism.

Baseline characteristics

The number of patients of the 11 included individual cohorts and registries varied from 21 to 204 patients (Table S1). All cohorts and registries were collected from 2001 and 2013. Nine of the 11 cohorts and registries were retrospectively collected and two were prospectively collected. In total, individual patient data of 945 patients were available, of which 6-month follow-up data were complete for 926 patients (98%) and these comprised the study patients for whom baseline characteristics are shown in **Table 1**. A total of 732 (79%) patients were treated with prolonged therapeutic LMWH, 100 (11%) patients were treated with VKA, 41 (4.4%) patients received another treatment (ie, inferior vena cava filter or unfractionated heparin), and 53 (5.7%) patients received no treatment.

Symptomatic recurrent VTE

Data regarding the occurrence of recurrent VTE were available from 10 of the 11 cohorts that included 857 patients, of whom 19 developed an objectively proven DVT and 22 recurrent PE (with or without DVT), and for three patients, the type of the recurrent VTE was unspecified. Nine (20%) of these 44 recurrent VTE occurred while anticoagulant treatment was discontinued: four events during temporary discontinuation of LMWH and five after treatment with LMWH was permanently stopped. Outcomes of the individual cohorts are avaliable in Table S2.

Table 1. Baseline characteristics of total cohort and stratified by management.

Treatment	Total cohort n=926 (100%)	LMWH n=732 (79%)	VKA n=100 (11%)	Other n=41 (4.4%)	None n=53 (5.7%)
Mean age (SD; range)	65 (12; 19-94)	64 (12; 19-94)	68 (12; 20-91)	68 (13; 28-90)	65 (14; 27-91)
Male sex, n (%)	491 (53)	378 (52)	60 (60)	22 (54)	31 (58)
Heart failure, n (%)	27/470 (5.7)	19/382 (5.0)	4/56 (7.1)	1/10 (10)	3/22 (14)
COPD, n (%)	35/471 (7.4)	25/383 (6.5)	7/56 (13)	0/10 (0)	3/22 (14)
Previous VTE, n (%)	47/566 (8.3)	32/435 (7.4)	10/86 (12)	1/13 (7.7)	4/32 (13)
Stage of malignancy, n (%)					
Metastatic cancer	501 (54)	400 (55)	56 (56)	12 (29)	33 (62)
Non-metastatic cancer	192 (21)	143 (20)	34 (34)	3 (7.3)	12 (23)
Unspecified	233 (25)	189 (26)	10 (10)	26 (63)	8 (15)
Type of malignancy, n (%)					
Lung	176 (19)	135 (18)	16 (16)	7 (17)	18 (34)
Colorectal	185 (20)	150 (20)	20 (20)	6 (15)	9 (17)
Other gastrointestinal	187 (20)	147 (20)	15 (15)	12 (29)	13 (25)
Breast	65 (7.0)	52 (7.1)	10 (10)	2 (4.9)	1 (1.9)
Gynaecological	64 (6.9)	56 (7.7)	5 (5.0)	3 (7.3)	0 (0)
Other or unknown	206 (22)	155 (21)	31 (31)	10 (24)	10 (19)
Haematological	43 (4.6)	37 (5.1)	3 (3.0)	1 (2.4)	2 (3.8)
Largest artery involved, n (%)					
Central	292 (32)	230 (31)	30 (30)	21 (51)	11 (21)
Segmental	301 (33)	238 (33)	35 (35)	7 (17)	21 (40)
Subsegmental	193 (21)	156 (21)	27 (27)	2 (4.9)	8 (15)
Unspecified	140 (15)	108 (15)	8 (8.0)	11 (27)	13 (25)

Note: COPD: chronic obstructive pulmonary disease; VTE: venous thromboembolism; LMWH: low molecular weight heparins; VKA: vitamin K antagonists.

Based on the intention-to-treat analysis, the weighted pooled 6-month risk of recurrent VTE was 6.2% (95% CI 3.5–12%) in patients treated with LMWH and 6.4% (95% CI 2.2–12%) in those who received VKA (**Table 2A, Figure 2**), with a HR adjusted for sex, age, type of cancer, and cancer stage of 0.92 (95% CI 0.3–3.1). In the 10 cohorts that reported data on recurrent VTE, a total of 42 (4.9%) patients did not receive any anticoagulant treatment, of whom four developed symptomatic VTE, resulting in a weighted pooled 6-month risk of 12% (95% CI 4.7–23%). Of these 42 patients, seven had a centrally located IPE, 18 had a segmental IPE, four had a subsegmental IPE, and in 13 patients, the thrombus location was unspecified. Of the four patients who did not receive anticoagulant treatment and developed a recurrent VTE, two had a subsegmentally located IPE and the other two had a segmentally located IPE. Compared with patients who were treated with either LMWH or VKA, the HR of symptomatic recurrent VTE in patients who did not

receive anticoagulant treatment was 2.0 (95% CI 0.65–5.9) adjusted for age, sex, type of cancer, and cancer stage. Outcomes stratified for cancer type are available in Table S3 .

The risk of recurrent VTE was non-significantly higher in patients with metastatic cancer at time of diagnosing IPE compared with those with non-metastatic cancer with a HR of 1.4 (95% CI 0.59–3.2) adjusted for age, sex, type of cancer, and management (Table S4). Regarding the location of the IPE, the weighted pooled 6-month risk of recurrent VTE was comparable in patients with a centrally located IPE compared with those with peripherally located IPE, 5.6% (95% CI 3.1–8.7%) and 6.6% (95% CI 3.5–11%), respectively, with a HR of 0.65 (95% CI 0.22–1.9) adjusted for age, sex, type of cancer, cancer stage, and management (Table S5). When patients with a subsegmental IPE were compared with those with a more centrally located IPE, incidence rates were 7.8% (95% CI 2.8–14.9%) and 5.5% (95% CI 2.9–8.8%), respectively, with a HR of 1.3 (95% CI 0.57–3.0) adjusted for age, sex, type of cancer, cancer stage, and management.

Based on the per-treatment analysis, the incidence rates of recurrent VTE were 12 per 100 patient years (PY) (31 events during 252 years of treatment; 95% CI 8.3–17) and 9.8 per 100 PY (3 events during 31 years of treatment; 95% CI 2.0–29) while receiving LMWH and VKA, respectively. For patients who did not receive anticoagulant treatment, either from the initial diagnosis or after LMWH or VKA were stopped within 6 months for reasons other than death, the incidence rate was 20 per 100 PY (nine events during 45 years of treatment; 95% CI 9.2–38) (**Table 2B**).

Table 2. Pooled outcomes after 6 months of follow-up for total cohort and stratified by management.
A: Pooled outcomes after 6 months of follow-up and stratified by initial management.

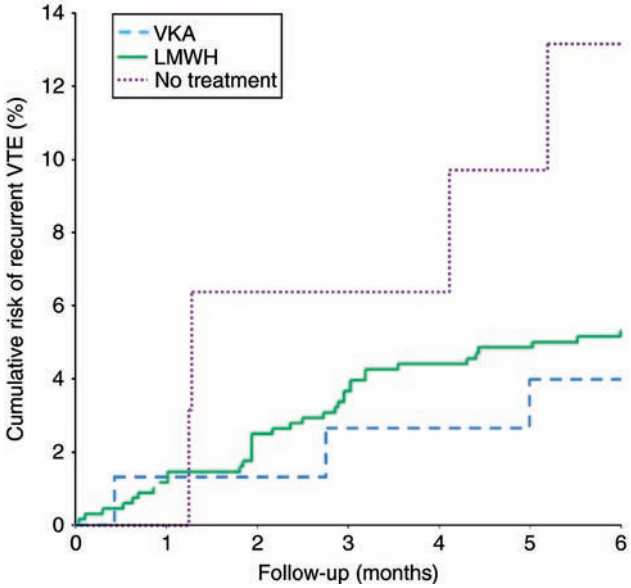
	Weight pooled risk in % (95%CI)				
Outcome	**Total cohort**	**LMWH**	**VKA**	**Other**	**None**
Recurrent VTE	5.8 (3.7-8.3)	6.2 (3.5-9.6)	6.4 (2.2-12)	4.3 (3.3-12)	12(4.7-23)
Major haemorrhage	4.7 (3.0-6.8)	3.9 (2.3-5.9)	13 (6.4-20)	6.4 (0.2-20)	6.4 (1.3-15)
Mortality	37 (28-47)	37 (29-44)	28 (18-40)	58 (38-77)	47 (28-66)

B: Incidence rates per 100 patient-years and stratified by management based on a per-protocol analysis.

	Weight pooled risk in % (95%CI)			
Outcome	**LMWH**	**VKA**	**Other**	**None**
Recurrent VTE	12 (8.3–17)	9.8 (2.0–29)	9.5 (0.24–53)	30 (8.2–77)
Major haemorrhage	10 (6.6–15)	26 (11–52)	18 (2.2–66)	4.6 (0.55–17)

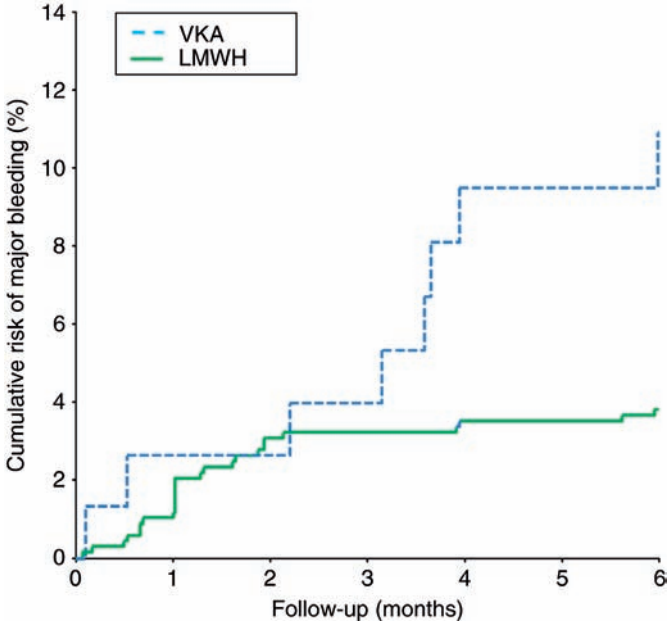
Note: VTE: venous thromboembolism; CI: confidence interval; VKA: vitamin K antagonist; LMWH: low molecular weight heparins.

Figure 2. Cumulative risk of recurrent venous thromboembolism related to management.



Note: VKA: vitamin K antagonists; LMWH: low molecular weight heparins. Based on a competing risk analysis.

Figure 3. Cumulative risk of major haemorrhage complications according to anticoagulant treatment.



Note: VKA: vitamin K antagonists; LMWH: low molecular weight heparins. Based on a competing risk analysis.

Major hemorrhage

Information regarding major hemorrhage was available for 10 cohorts concerning a total of 857 patients of whom 38 patients experienced a major hemorrhage. Overall weighed pooled incidence rates are provided in **Table 2**. The risk of major hemorrhage was comparable in patients with metastatic and non-metastatic cancer and in patients with a centrally located IPE compared with those with a peripherally located IPE, with a HR of 1.8 (95% CI 0.68–4.8) adjusted for age, sex, type of cancer, and management and 1.0 (95% CI 0.31–3.0), adjusted for age, sex, type of cancer, cancer stage, and management (Tables S4 and S5).

Based on the intention-to-treat analysis, the weighted pooled 6-month risk of major hemorrhage was significantly higher in patients treated with VKA compared with those treated with LMWH, 13% (95% CI 6.4–20%) versus 3.9% (95% CI 2.3–5.9%) with a HR of 4.0 (95% CI 1.5–10) adjusted for age, sex, type of cancer, and cancer stage (**Table 2A, Figure 3**). The weighted 6-month pooled risk of major hemorrhage in patients who were left untreated was 6.4% (95% CI 1.3–15%). Based on the per-treatment analysis, the incidence rate of major hemorrhage while receiving VKA treatment was 26 per 100 PY (eight events during 30 years of treatment; 95% CI 11–52), and while receiving LMWH treatment, the incidence rate was 10 per 100 PY (26 events during 257 years of treatment; 95% CI 6.6–15) (**Table 2B**).

Mortality

Of the 926 patients, 331 died during follow-up, resulting in a weighted pooled 6-month mortality of 37% (95% CI 28–47%; **Table 2A**). Mortality varied between cancer type and cancer stage (Tables S3 and S4). The weighted pooled 6-month mortality was higher in patients with a centrally located IPE compared with those with a peripherally located IPE: 42% (95% CI 33–52%) versus 30% (95% CI 25–36%) with a HR of 1.5 (95% CI 1.1–2.0) adjusted for age, sex, type of cancer, cancer stage, and management. Patients with a centrally located IPE more frequently had metastatic cancer (79%) compared with those with a more peripherally located IPE (67%) (χ^2 test: $P < 0.01$).

The weighted pooled 6-month mortality was 37% (95% CI 29–44%) in patients treated with LMWH and 28% (95% CI 18–40%) in those treated with VKA (HR 1.1; 95% CI 0.70–1.6 adjusted for age, sex, cancer type, and cancer stage). In patients who did not receive any treatment, the weighted pooled 6-month mortality was 47% (95% CI 28–66%).

DISCUSSION

This study of individual patient data of 926 patients from 11 registries is the largest study on cancer-associated IPE thus far and provides several important new findings.

First, this study demonstrates a 6-month VTE recurrence risk of 12% (95% CI 4.7–23%) in patients who were left untreated. Although it is possible that these patients were left

untreated for a specific reason, that is, a high risk of hemorrhage, a poor overall prognosis, or a supposed low risk of recurrent VTE, the patient's characteristics did not differ greatly from those of treated patients. Importantly, the higher mortality in the untreated patients may even have resulted in an underestimation of the pooled 6-month VTE recurrence risk due to significant competing risk of death. In the per-treatment analysis, the incidence rate of recurrent VTE in patients who did not receive anticoagulant treatment was even 30 per 100 PY (95% CI 8.2–77). Thus, this observation emphasizes the high risk of symptomatic recurrent VTE in cancer patients with IPE and recalls the effect size of anticoagulants used in SPE, thereby supporting the initiation of anticoagulation in cancer-associated IPE [5, 6].

Second, we observed a comparable efficacy of VKA and LMWH with a significantly higher risk of major hemorrhage in patients who were treated with VKA. Although these findings should be interpreted with caution due to the observational study design and the lack of information about the quality of anticoagulant treatment, it seems unlikely that patients with a high risk of major hemorrhage were predominantly assigned to receive VKA. This is reflected by the comparable baseline characteristics of both groups and by the non-significantly lower mortality in patients treated with VKA. Notably, a comparable risk of major hemorrhage between oral and parenteral anticoagulants has been demonstrated in cancer patients with proven clinically suspected PE, while the recurrence risk was lower in those treated with LMWH [29]. This notable difference between the efficacy and safety of oral versus parenteral anticoagulants in IPE and SPE may be caused by the observational design of our study in which all cancer patients with IPE were included, whereas patients with a high risk of major hemorrhage were excluded from the trials in cancer patients with SPE. A second explanation could be poor quality of anticoagulant treatment, on which information was unfortunately unavailable for our study subjects. However, the comparable risk of recurrent VTE in patients treated with VKA and LMWH argues against a poor quality of anticoagulant management. Regardless, the observations from the current study supports LMWH as treatment of choice for cancer-associated VTE [5, 6].

Given the debate regarding the clinical relevance of isolated subsegmental SPE, the clinical significance and management of subsegmental IPE may be even less clear [30, 31]. Therefore, the comparable risk of recurrent VTE in cancer patients with a subsegmental IPE versus more centrally located IPE and the observation of recurrent events in untreated patients with subsegmental IPE are further key findings of this study. Both observations argue against subsegmental IPE as a distinct disease entity and support an identical management. Since the presence of (asymptomatic) DVT in patients with a subsegmental IPE was not investigated in the cohorts, conclusions regarding the clinical relevance of isolated subsegmental IPE can not be drawn. The finding that subsegmental PE is not associated with a more favorable prognosis with regard to VTE recurrences

was recently described in non-cancer patients with SPE as well [32]. Notably, in line with the observation of O'Connell and colleagues, centrally located IPE was associated with a higher mortality than distally located PE in the current analysis [24]. Two likely explanations for this phenomenon could be a higher mortality directly related to VTE, as observed for SPE, or a higher cancer-related mortality [33].

Strengths of this study are the systematic literature search for potential studies and ongoing registries; the high number of included patients, far exceeding previously published cohorts; the strict and identical diagnostic criteria for IPE among the included studies and registries; the reporting of objectively established outcomes; and the use of patient-level data.

The most relevant limitation of this study is related to the observational and predominantly retrospective designs of the individual registries and the unavailability of results from nine identified cohorts that may have introduced selection bias. Since four cohorts were only described in a meeting abstract and the risk of recurrent VTE is only described for one of five cohorts published in a peer-reviewed journal, our study seems to be a good representation of existing literature. It should be mentioned that patients were not randomly assigned to treatment and no uniform management protocol was applied, and it is unknown whether the presence of asymptomatic DVT had been investigated and influenced management decisions. Also, initial CT results and outcomes were not adjudicated by an independent committee. The impact of ongoing oncologic management (e.g., systemic chemotherapy) and its potential contribution to the risk of recurrent VTE and/or cancer related prognosis are additional confounding factors that cannot fully be accounted for in this study. Due to the study design, we were unable to provide a reliable estimation of the burden of recurrent VTE on mortality. Ideally, a randomized clinical trial should be performed to provide more definite answers. However, given all available evidence to date, we consider conducting a randomized clinical trial allocating patients with cancer-associated IPE to placebo or anticoagulant treatment as ethically very challenging. This is supported by the results of the enquiry among physicians, of whom 89–100% judged treatment of cancer-associated IPE to be necessary [34].

In conclusion, this study demonstrates a substantial risk of symptomatic recurrent VTE in cancer patients with IPE and suggests an even higher recurrence risk when anticoagulant treatment is withheld. An LMWH-based treatment regimen was associated with a lower risk of major hemorrhage than treatment with VKAs. These observations support the current guideline recommendations to initiate anticoagulant treatment with LMWH for cancer-associated VTE. Finally, our data argue against different management of subsegmental cancer-associated IPE.

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CHAPTER 12

General Discussion and summary

The studies described in this thesis aim to improve both the diagnostic strategy in patients with suspected pulmonary embolism as well as the therapeutic management in patients with proven acute pulmonary embolism. **Chapter 1** consists of a general introduction and overview of the presented studies. **Chapter 2** gives an overview of the currently available diagnostic strategies for clinically suspected acute pulmonary embolism and the treatment of acute pulmonary embolism. The different clinical decision rules, the D-dimer test and the different imaging tests will be discussed. Furthermore, the current situation concerning the treatment of acute pulmonary embolism including risk stratification, the possibility of outpatient treatment, indications for thrombolysis, the available anticoagulants and the optimal duration of treatment will be addressed.

Part I: Diagnostic management in suspected pulmonary embolism

Chapter 3 discusses the results of a systematic review and patient-level meta-analysis on the efficiency and safety of the exclusion of pulmonary embolism based on a Wells score combined with D-dimer testing. This is the most applied diagnostic strategy to exclude pulmonary embolism without an imaging test worldwide. The results of this study confirm results of earlier studies that proved the efficiency and safety of this strategy for the total group of patients. What this study adds, is the confirmation of the safety of the strategy in different clinically relevant subgroups: inpatients, patients with cancer, chronic obstructive pulmonary disease and venous thromboembolism in their medical history and patients who present themselves late to the clinician. In all groups, the risk of a venous thromboembolism was less than 3 % during 3 months after the initial exclusion of pulmonary embolism based on the Wells score and a D-dimer test. Also, it was shown that the use of an age-adjusted D-dimer threshold (calculated by multiplying the patients age by ten for patients over 50 years of age) instead of the fixed threshold of 500 µg/L fot the total group leads to an increase of patients in whom pulmonary embolism could be ruled out without an imaging test from 28% to 33%. Finally, it is mentioned that the profits of the application of the age-adjusted D-dimer threshold differs between subgroups, being logically the highest in the older patients.

In **chapter 4**, the safety of exclusion of pulmonary embolism based on a normal CTPA is examined. For most patients, the safety of a normal CTPA is undisputed, but in patients with a high pre-test probability, this remains controversial in literature. To clarify this issue, the results of 4 earlier studies on the safety and efficiency of the diagnostic management of suspected pulmonary embolism were combined. This study confirmed that in the total group of patients, the risk of venous thromboembolism after a normal CTPA is very low: 2.0% during the first 3 months. In specific patient groups however, the risk of venous thromboembolism is higher, despite a normal CTPA: this concerns patiens with a very high pre-test probability (Wells score >6), patients with complaints of deep venous thrombosis and patients with a malignancy.

It is difficult to determine whether and to which extent this higher risk is caused by missed diagnoses of venous thromboembolism at presentation of by newly developed venous thromboembolism in the period thereafter. A strategy to diminish the risk of venous thromboembolism is also unclear.

The following two chapters set out two studies that investigated improvement of the diagnostic process in suspected pulmonary embolism. In **chapter 5** the possibility of applying a higher D-dimer threshold in patients with a low pre-test probability was examined, using the combined results of two earlier studies. Instead of the dichotomous algorithm, the trichotomous algorithm based on the Wells score was used. In patients with a low pre-test probability of PE, based on a Wells score of <2 points, a D-dimer threshold of <1000 µg/L was used; in patients with a moderate pre-test probability, based on a Wells score of 2-6 points, the D-dimer threshold was <500 µg/L and only in patienst with a high risk on PE based on a Wells score of >6 points, a CTPA was performed directly. The results show that this strategy leads to improved efficiency in the diagnostic process: the percentage of patients in whom PE could be excluded without a CTPA rises from 26% to 36%. The number of missed diagnoses of PE seems to be small, though it requires a prospective validation study to confirm this.

Chapter 6 shows the results of the YEARS study: a prospective validation study of a highly simplified diagnostic algorithm for suspected PE. In the YEARS algorithm, the Wells score was replaced by three YEARS items: clinical signs of deep veen thrombosis, hemopthysis and whether the treating clinician thinks pulmonary embolism is the most probable diagnosis. These items are scored, and subsequently a D-dimer test is performed in all patients. When no YEARS item is present and the D-dimer result is <1000 µg/L, PE is excluded without the use of CTPA. In patients with one or more YEARS items, the D-dimer threshold is set at <500 µg/L to be able to exclude PE without a CTPA. This algorithm wat tested prospectively in the YEARS study in 3465 patients. Results reveal that this algorithm can be applied safely: the risk of venous thromboembolism after exclusion of PE was only 0.61%. Benefits of the YEARS algorithm are the simplified procedure: there are only three items to score and in all patients a D-dimer test can be performed instead of only those with an unlikely pre-test probabilty. The main benefit, however, is the 14% increase of the the number of patients who can be managed safely without a CTPA in comparison with the standard algorithm, 48% versus 34% respectively.

Part II: Treatment of acute pulmonary embolism

In the treatment of pumonary embolism and deep venous thrombosis, one of the most important developments of the past years is the introduction of the direct oral anticoagulants. These oral drugs directly inhibit thrombine (factor IIa) or factor Xa. Their largest benefit is a more stable famockinetic and farmacodynamic profile, which makes routine evaluation of the anticoagulant effect, as in vitamin K antagonists, not required.

Also, several studies report lower risks of bleeding complications. **Chapter 7** describes a meta-analysis of individual studies of the direct oral anticoagulants for the treatment of acute PE and deep venous thrombosis. The results confirm that direct oral anticoagulants are equally effective in the prevention of recurrent venous thromboembolism with a relative risk of 0.88 (95% confidence interval 0.74-1.05). Also, this meta-analysis confirms the indication of a lower risk of bleeding complications when direct oral anticoagulants are used: the relative risk of major bleeding is 0.60 (95% confidence interval 0.41-0.88). It should be emphasized, however, that the absolute risks of both recurrent venous thromboembolism and major bleeding are small, and therefore so are the differences between absolute risks.

In **chapter 8**, a very specific recommendation from the Dutch Guideline on Diagnostics, Prevention and Treatment of Venous Thromboembolism and Secondary Prevention Arterial Thrombosis is evaluated. In general, it is costumary to advise anticoagulant treatment for indefinite duration to all patients who have had a second venous thromboembolism. However, the guideline also advises to consider limited duration of treatment of twelve months in patients in whom the second thromboembolism appeared more than one year after the cessation of anticoagulant treatment for the first event. There was solely indirect evidence fort his recommendation. This chapter reveals the outcomes of the application of this specific recommendation in the Leiden Universitry Medical Centre. Of 131 patients with second venous thromboembolism more than one year after stopping anticoagulant treatment, 77 patients were treated for a limited duration. After stopping anticoagulant treatment, the incidence of venous thromboembolism was 9.4 per 100 patientyears (95% confidence interval 6.1-14), and the risk seems even higher in patients with an idiopathic second venous thromboembolism and lower in those with a provoked venous thromboembolism. Although this is an observational study, it is highly probable that this high risk of recurrent venous thromboembolism exceeds the risk of continuing anticoagulant treatment, mainly bleeding complications. Therefore, this study does not support the recommendation of the Dutch Guideline.

The three chapters that follow adress the treatment of cancer-associated venous thromboembolism. In **chapter 9**, a cohort study is described which evaluates the safety of stopping anticoagulant treatment in cancer-assiciated venous thromboembolism in patients cured from cancer. Out of 358 included patients with cancer-associated venous thromboembolism, anticoagulant treatment could be discontinued in 68 patients after they were cured from their malignancy. The risk of recurrent venous thromboembolism in this group was low with an incidence of 3.2 per 100 patientyears (95% confidence interval 1.5-5.9). Notable in this study is the observation that in 7 out of the 10 patients with recurrent venous thromboembolism, a recurrence of the malignancy was observed at the same moment or shortly after the diagnosis of recurrent venous thromboembolism. These results support the current guideline to discontinue anticoagulant treat-

ment for cancer-associated venous thromboembolism in patients cured from cancer. **Chapter 10** outlines a meta-analysis of the use of direct oral anticoagulants voor cancer-associated venous thromboembolism. The method of this study is identical to the study described in chapter 7, but in this chapter the focus was on cancer-associated venous thromboembolism only. A total of 19,060 patients were included in the five separate studies, of which 973 were known to have an active malignancy. The risks of recurrent venous thromboembolism and bleeding complications were relatively high, compared to patients without cancer, which is in accordance with current literature. The relative risk for recurrent venous thromboembolism for direct oral anticoagulants compared to vitamin K antagonists was 0.66 (95% confidence interval 0.38-1.2) and the risk for major and clinically relevant bleeding 0.94 (95% confidence interval 0.70-1.3). It must be mentioned that little information was provided about the nature and dissemination of the cancer as well as anti-cancer treatment. Furthermore, the treatment in the control arm of this study, vitamin K antagonists, is not the treatment of first choice in cancer-associated venous thromboembolism. For these reasons, the results of this study should be interpreted cautiously. The results may serve as a strong stimulant to investigate direct oral anticoagulants in the treatment of cancer-associated venous thromboembolism, which is currently underway.

Chapter 11 finally focuses on coincidental diagnosed pulmonary embolism, generally referred to as incidental pulmonary embolism. This is a relatively new clinical presentation predominantly seen in cancer patients, due to the relatively high risk of venous thromboembolism and by the frequent performance of high quality CT-scanning in these patients. Based on observational, often small studies it is recommended to treat incidental pulmonary embolism in the same way as clinically suspected pulmonary embolism. This chapter aimed to collect as much data as possible out of the individual observational studies in order to find the best available evidence on the treatment of incidental pulmonary embolism. Information concerning a total of 926 patients out of 11 different studies was collected. The most important results include a comparable risk of recurrent venous thromboembolism in patients treated with low molecular weight heparins compared to vitamin K antagonists: 6.2% vs 6.4% during 6 months after the diagnosis. The risk in 53 patients who were not treated with anticoagulant treatment, for which the reason was unknown, was 12%. The risk of major bleeding was considerably higher in patients treated with vitamine K antagonists: 13% versus 3.9% in the group treated with low molecular weight heparins. Despite several important limitations due to study design, these results suggest that anticoagulant treatment lowers the risk of recurrent venous thromboembolism and that low molecular weight heparins are favourable over vitamin K antagonists. Both conclusions support the recommendations of current guidelines.

Perspective for the future

A diagnostic algorithm such as the YEARS algorithm allows clinicians to exclude pulmonary embolism in patients in which they suspect pulmonary embolism, without the use of potentially harmfull CTPA. For the future, it remains a challenge to further diminish the need for CTPA. It does not seem to be very likely however that any more profit can be achieved from alterations in the clinical decision rule or D-dimer thresholds.

Perhaps, in the future CTPA can be replaced by alternative imaging such as an MRI scan, to overcome concerns on radiation exposure. For now, the low sensitivity and high risk of inconclusive results are the most important limitations of MRI scanning for suspected PE. Another challenge for the future is the suspicion of pulmonary embolism in pregnant women. This is a relatively common clinical challenge, in which the risk of radiation exposure for the unborn child forms an extra concern and argument to make an effort to reduce the use of CTPA. Untill now, no diagnostic strategy was validated to exclude pulmonary embolism in pregnant women without an imaging test, emphasizing the urgent need for a prospective study of an algorhitm such as the YEARS algorhitm in this group.

The introduction of the direct oral anticoagulant poses several important unanswered questions concerning the optimal treatment of acute pulmonary embolism. These drugs have now become the treatment of choice for the majority of patients with acute pulmonary embolism. In cancer patients, the efficacy and safety of these drugs is being investigated. Also, the low risk of bleeding complications has influence on the risk-benefit ratio of extending anticoagulant treatment. Therefore, the introduction of these drugs may have consequences for the choices on the duration of treatment. Clinicians and patients will tend to continuing anticoagulant treatment indefinitely, also for a first episode of venous thromboembolism, due to the lower bleeding risks. This will have important consequences and will lead to higher health care costs and over-treatment, since many patients never develop a recurrent venous thromboembolism. Furthermore, it is interesting whether the risk of a recurrent event evolves over time: does anticoagulant treatment prevent a recurrence only during therapy, or does the risk decline over time, which creates a possibility to stop anitocagulant treatment later on?

In incidental pulmonary embolism, the advantage of anticoagulant treatment remains unclear. Indirect evidence, as in this thesis, suggests a lower risk of recurrent venous thromboembolism when treated, and therefore a benefit for patients. Cancer patients, however, are also known to have a considerably higher risk of bleeding complications during anticoagulant treatment. A definite answer to this question requires a randomized trial directly comparing no or only very short duration of treatment to indefinite duration of treatment, but such a trial will probably never be performed.

CHAPTER 13

Nederlandse samenvatting

De studies beschreven in dit proefschrift zijn gericht op het verbeteren van de diagnostiek bij patiënten met een klinische verdenking op acute longembolie en het optimaliseren van de behandeling van patiënten met bewezen acute longembolie. **Hoofdstuk 1** bevat een algemene introductie en een overzicht van de studies in dit proefschrift. **Hoofdstuk 2** betreft een uitgebreid overzicht van de huidige diagnostiek bij verdenking op acute longembolie en de behandeling. Hierbij komen de verschillende klinische beslisregels, de D-dimeer test en het radiologisch onderzoek aan de orde. Wat betreft de behandeling van bewezen acute longembolie worden de huidige stand van zaken betreffende risicostratificatie, de mogelijkheid van thuisbehandeling, de indicaties voor trombolyse, de beschikbare antistollingsbehandeling en de optimale behandelduur besproken.

Deel 1: Diagnostiek bij verdenking acute longembolie

In **hoofdstuk 3** worden de resultaten beschreven van een systematische review en individuele patiënten-data meta-analyse naar de efficiëntie en veiligheid van het uitsluiten van longembolie op basis van een Wells score in combinatie met de D-dimeer test. Dit is wereldwijd de meest gebruikte strategie voor het uitsluiten van longembolie zonder het verrichten van radiologisch onderzoek. De resultaten van deze studie bevestigen de resultaten van eerdere studies waarin de veiligheid en efficiëntie van deze strategie voor de totale groep patiënten was aangetoond. In aanvulling op de individuele studies bevestigt deze studie de veiligheid van de strategie in verschillende klinisch relevante subgroepen, te weten klinische patiënten, patiënten met kanker, chronische obstructieve longziekte (COPD), veneuze trombo-embolie in de voorgeschiedenis en patiënten die zich relatief laat hebben gepresenteerd. In alle groepen was het risico op veneuze trombo-embolie minder dan 3% gedurende 3 maanden nadat longembolie was uitgesloten op basis van de Wells score en de D-dimeer test. Daarnaast toont deze studie dat gebruik van de leeftijdsafhankelijke D-dimeer afkapwaarde (te berekenen door de leeftijd van een patiënt te vermenigvuldigen met 10 voor patiënten ouder dan 50 jaar) in plaats van een vaste afkapwaarde van 500 µg/L voor de totale groep leidt tot een toename van 28% naar 33% van de patiënten waarbij longembolie kan worden uitgesloten zonder het verrichten van radiologisch onderzoek. Ten slotte laat de studie zien dat de winst van de leeftijdsafhankelijke D-dimeer afkapwaarde verschilt tussen belangrijke subgroepen, waarbij de winst logischerwijs voornamelijk gezien wordt bij patiënten op hogere leeftijd. **Hoofdstuk 4** heeft betrekking op de veiligheid van het uitsluiten van longembolie op basis van een normale CT-scan. Voor de meeste patiënten met een normale CT-scan is de veiligheid onomstreden, maar voor patiënten met een hoge voorafkans op longembolie is de veiligheid van een normale CT-scan nog altijd omstreden in de literatuur. Om dit te onderzoeken werden de resultaten van 4 eerder verrichte studies naar de veiligheid en efficiëntie van de diagnostiek bij verdenking

longembolie gecombineerd. De resultaten van deze studie bevestigde dat voor de totale groep patiënten waarbij longembolie wordt uitgesloten door middel van een normale CT-scan het risico op veneuze trombo-embolie erg laag is, namelijk 2,0% gedurende de 3 maanden nadien. Echter in specifieke patiëntgroepen is er sprake van een hoger risico op veneuze trombo-embolie ondanks een normale CT-scan, in het bijzonder patiënten met een zeer hoge vooraf kans (op basis van een Wells score >6 punten), patiënten met klachten verdacht voor een diep veneuze trombose en patiënten met kanker. Het is echter niet vast te stellen of en in welke mate dit hogere risico wordt veroorzaakt door gemiste diagnoses van veneuze trombo-embolie bij presentatie of door nieuw ontwikkelde veneuze trombo-embolie in de periode nadien. Ook is het onduidelijk hoe dit risico op veneuze trombo-embolie verlaagd zou kunnen worden.

In de twee volgende hoofdstukken worden 2 studies beschreven waarin onderzocht is of de diagnostiek bij verdenking longembolie verder verbeterd kan worden. In **hoofdstuk 5** wordt een studie beschreven welke heeft onderzocht of het mogelijk is de D-dimeer afkapwaarde te verhogen in patiënten met een lage voorafkans op longembolie. Hiervoor werden de resultaten van 2 eerder verrichte studies gebruikt. In plaats van de dichotome algoritme werd het trichotome algoritme op basis van de Wells score gebruikt. Voor patiënten met een lage vooraf kans op longembolie op basis van een Wells score <2 punten werd een D-dimeer afkapwaarde van <1000 µg/L gebruikt, in patiënten met een matig risico op longembolie op basis van een Wells score van 2-6 punten werd een D-dimeer afkapwaarde van <500 µg/L gebruikt en alleen patiënten met een hoog risico op longembolie op basis van een Wells score >6 punten werd direct een CT-scan verricht. De studie laat zien dat deze strategie leidt tot een verbetering van de efficiëntie van de diagnostiek, het percentage van de patiënten waarbij longembolie kan worden uitgesloten zonder CT-scan stijgt van 26% naar 36%. Tevens laat de studie zien dat dit mogelijk zal leiden tot een klein aantal gemiste diagnoses longembolie, maar om vast te stellen of dit inderdaad het geval zal zijn is een prospectieve validatie studie noodzakelijk. In **hoofdstuk 6** worden de resultaten van de YEARS studie beschreven. Dit betreft een prospectieve validatie studie van een sterk vereenvoudigd diagnostisch algoritme voor verdenking longembolie. In het YEARS algoritme is de Wells score vervangen door slechts 3 YEARS items, te weten: klinische tekenen van diep veneuze trombose, hemoptoë en of een longembolie de meest waarschijnlijke diagnose is volgens de verantwoordelijk arts. Vervolgens wordt bij alle patiënten een D-dimeer test verricht. Wanneer geen van de YEARS items aanwezig is en de D-dimeer concentratie <1000 µg/L is kan een longembolie worden uitgesloten zonder het verrichten van een CT-scan. Voor patiënten waarbij één of meer van de YEARS items aanwezig is moet er sprake zijn van een D-dimeer concentratie <500 µg/L om een longembolie uit te kunnen sluiten zonder het verrichten van een CT-scan. In de YEARS studie is dit algoritme prospectief onderzocht in 3465 patiënten. De studie heeft aangetoond dat dit algoritme

veilig kan worden toegepast: het risico op veneuze trombo-embolie nadat longembolie was uitgesloten was slechts 0,61%. Het voordeel van het YEARS algoritme is de sterke vereenvoudiging van de diagnostiek, in plaats van de bestaande Wells score hoeven nu maar 3 items te worden bekeken en in alle patiënten kan direct een D-dimeer test worden verricht in plaats van alleen in patiënten met een lage voorafkans op longembolie. De grootste winst van het YEARS algoritme is echter de grote toename van het percentage patiënten waarbij longembolie kan worden uitgesloten zonder CT-scan. In vergelijking met het meest gebruikte algoritme bestaande uit de Wells score en een D-dimeer afkapwaarde van <500 µg/L leidt het YEARS algoritme tot een toename van 34% naar 48% van de patiënten waarbij longembolie kan worden uitgesloten zonder CT-scan, een verschil van 14%.

Deel 2: Behandeling van bewezen acute longembolie

Een van de belangrijkste ontwikkelingen van de afgelopen jaren met betrekking op de behandeling van longembolie en diep veneuze trombose betreft de introductie van de directe orale anticoagulantia. Deze orale middelen remmen direct trombine (factor IIa) of factor Xa en hebben als grootste voordeel een stabielere farmacokinetiek en farmacodynamiek, waardoor routinematige controle van het antistollingseffect zoals bij het gebruik van vitamine K antagonisten niet noodzakelijk is. Daarnaast lijkt er sprake van lager risico op bloedingscomplicaties in de afzonderlijke studies. In **hoofdstuk 7** wordt een meta-analyse beschreven van de individuele studies van de directe orale anticoagulantia voor de behandeling van acute longembolie en diep veneuze trombose. De resultaten van de meta-analyse bevestigen dat de directe orale anticoagulantia even effectief zijn in het voorkomen van een recidief veneuze trombo-embolie met een relatief risico van 0,88 (95% betrouwbaarheidsinterval 0,74-1,05). Tevens bevestigt de meta-analyse de aanwijzingen uit de individuele studies dat het risico op bloedingscomplicaties lager is bij gebruik van de directe orale anticoagulantia. Zo is het relatief risico op majeure bloedingscomplicaties 0,60 (95% betrouwbaarheidsinterval 0,41-0,88). Overigens dient vermeld te worden dat de absolute risico's op zowel een recidief veneuze trombo-embolie als een majeure bloeding klein zijn en daarmee het verschil in absolute risico's relatief klein is.

In **hoofdstuk 8** wordt een heel specifieke aanbeveling uit de Nederlandse richtlijn Diagnostiek, Preventie en Behandeling van Veneuze Trombo-Embolie en Secundaire Preventie Arteriële Trombose onderzocht. In het algemeen kan gesteld worden dat het wereldwijd gebruikelijk is om patiënten met een recidief veneuze trombo-embolie te adviseren om de antistollingstherapie levenslang te continueren. In de genoemde Nederlandse richtlijn wordt echter geadviseerd om bij patiënten waarbij het recidief veneuze trombo-embolie meer dan 1 jaar het staken van de antistollingstherapie voor de eerste veneuze trombo-embolie is opgetreden een beperkte behandelduur van 12

maanden te overwegen. Voor deze aanbeveling bestond echter alleen indirect bewijs. In hoofdstuk 8 worden de uitkomsten beschreven van het toepassen van deze aanbeveling in het Leids Universitair Medisch Centrum. Van de 131 patiënten met een recidief veneuze trombo-embolie meer dan 1 jaar het staken van de antistollingstherapie die werden geïncludeerd in de studie werden 77 patiënten voor een beperkte duur behandeld. Na staken van de antistollingstherapie was het incidentie cijfer voor veneuze trombo-embolie 9,4 per 100 patiëntjaren (95% betrouwbaarheidsinterval 6,1-14) waarbij het risico in patiënten met een idiopathische tweede veneuze trombo-embolie nog hoger lijkt en het risico in patiënten met een uitgelokte tweede veneuze trombo-embolie lager. Hoewel het een observationele studie betreft is het zeer aannemelijk dat dit hoge risico op een recidief veneuze trombo-embolie de risico's, met name bloedingscomplicaties, van het continueren van de antistollingstherapie overtreft. Daarmee biedt deze studie geen ondersteuning voor deze specifieke aanbeveling in de Nederlandse richtlijn.

De volgende drie hoofstukken hebben betrekking op de behandeling van kanker-geassocieerde veneuze trombo-embolie. In **hoofdstuk 9** wordt een cohort studie beschreven waarbij met name onderzocht is of het veilig is om de antistollingstherapie voor een kanker-geassocieerde veneuze trombo-embolie te staken in patiënten die genezen zijn van kanker. Van de 358 geïncludeerde patiënten met een kanker-geassocieerde veneuze trombo-embolie kon de antistollingstherapie gestaakt worden in 68 patiënten nadat zij genezen waren van kanker. Het risico op een recidief veneuze trombo-embolie in deze patiënten was laag met een incidentie cijfer van 3,2 per 100 patiëntjaren (95% betrouwbaarheidsinterval 1,5-5,9). Opvallend hierbij is dat bij 7 van de 10 patiënten met een recidief veneuze trombo-embolie ook een recidief van de kanker werd vastgesteld voor of kort na de diagnose recidief veneuze trombo-embolie. Deze studie ondersteunt de huidige richtlijn om de antistollingstherapie voor kanker-geassocieerde veneuze trombo-embolie te staken in patiënten die genezen zijn van kanker. In **hoofdstuk 10** wordt een meta-analyse beschreven naar het gebruik van de directe orale anticoagulantia voor kanker-geassocieerde veneuze trombo-embolie. De methode van deze studie is identiek aan de methode van de studie uit hoofdstuk 7, maar nu is voor de resultaten specifiek gekeken naar patiënten met een kanker-geassocieerde veneuze trombo-embolie. In de vijf afzonderlijke studies zijn in totaal 19.060 patiënten geïncludeerd waarvan er 973 bekend waren met een actieve kanker. In vergelijking met patiënten zonder actieve kanker waren het risico op een recidief veneuze trombo-embolie en bloedingscomplicaties relatief hoog, wat overigens geheel in overeenkomst is met bestaande literatuur. Het relatief risico voor directe anticoagulantia vergeleken met vitamine K antagonisten voor recidief veneuze trombo-embolie was 0,66 (95% betrouwbaarheidsinterval 0,38-1,2) en voor majeure en klinisch relevante bloedingen 0,94 (95% betrouwbaarheidsinterval 0,70-1,3). Belangrijk om hierbij te vermelden is dat er zeer beperkte informatie beschikbaar was over de soort, uitgebreidheid en de behandeling voor de kanker. Daarnaast is

de behandeling in de controle arm, vitamine K antagonisten, niet de behandeling van eerste keuze voor kanker-geassocieerde veneuze trombo-embolie. Om deze redenen dienen de resultaten van deze studie voorzichtig geïnterpreteerd te worden. Wel dienen ze als sterke aansporing om de directe anticoagulantia te onderzoeken voor de behandeling van kanker-geassocieerde veneuze trombo-embolie, wat overigens op dit moment ook gebeurt. **Hoofdstuk 11** richt zich tenslotte op bij toeval gevonden longembolie, dit is een relatief nieuwe klinische presentatie voornamelijk optredend bij patiënten met kanker. Dit wordt veroorzaakt door het relatief hoge risico op veneuze trombo-embolie in patiënten met kanker en door het frequent toepassen van steeds van betere kwaliteit zijnde CT-scans in deze patiëntengroep. Op basis van observationele, veelal kleine studies wordt geadviseerd bij toeval gevonden longembolie hetzelfde te behandelen als longembolie vastgesteld bij patiënten waarbij een klinische verdenking bestond. In hoofdstuk 11 is getracht om zoveel mogelijk gegevens van individuele observationele studies te verzamelen om daarmee het best beschikbare bewijs betreffende de behandeling van bij toeval gevonden longembolie te verkrijgen. In totaal werden gegevens van 926 patiënten uit 11 verschillende studies verzameld. De belangrijkste resultaten van deze studie waren een vergelijkbaar risico op een recidief veneuze trombo-embolie onder behandeling met laag moleculair gewicht heparine en vitamine K antagonisten, respectievelijk 6,2% en 6,4% gedurende 6 maanden na diagnose. Het risico in 53 patiënten die om onbekende reden niet zijn behandeld met antistollingstherapie was 12%. Het risico op majeure bloedingen was aanzienlijk hoger onder behandeling met vitamine K antagonisten, 13% vergeleken met 3,9%. Ondanks een aantal belangrijke beperkingen ten gevolge van de studie opzet suggereert deze studie dat antistollingstherapie het risico op een recidief veneuze trombo-embolie verlaagt en dat laag moleculair gewicht heparine de voorkeur verdient boven vitamine K antagonisten. Beide ondersteunen de aanbevelingen in de huidige richtlijnen.

Toekomstperspectief

Een diagnostisch algoritme zoals het YEARS algoritme stelt artsen in staat om bij een steeds groter gedeelte van de patiënten met een klinische verdenking op longembolie de diagnose uit te sluiten zonder het verrichten van een potentieel schadelijke CT-scan. Het blijft een uitdaging voor toekomstig onderzoek om de noodzaak voor het verrichten van een CT-scan verder terug te dringen. Het is echter niet te verwachten dat er nog een grote winst behaald kan worden door verdere aanpassingen aan een klinische beslisregel of de D-dimeer afkapwaarden. Wellicht dat in de toekomst de CT-scan vervangen kan worden door een alternatief radiologisch onderzoek zoals de MRI-scan, zodat in ieder geval de zorgen over stralenbelasting weggenomen kunnen worden. Vooralsnog zijn de relatief lage sensitiviteit en een hoog percentage onduidelijke uitslagen hiervoor de belangrijkste beperkingen. Een andere uitdaging vormt de patiëntengroep zwangere

vrouwen waarbij een klinische verdenking op longembolie bestaat. Dit is een relatief frequent voorkomende situatie waarin naast de zorgen over stralenbelasting voor de vrouw ook de stralenbelasting voor het ongeboren kind reden zijn om te streven het gebruik van de CT-scan te reduceren. Tot op heden is er geen enkele diagnostische strategie waarbij longembolie werd uitgesloten zonder radiologisch onderzoek gevalideerd in zwangere vrouwen. Aan een prospectieve studie in deze groep naar een diagnostisch algoritme zoals het YEARS algoritme is dringend behoefte.

Enkele belangrijke onbeantwoorde vragen met betrekking tot de optimale behandeling van acute longembolie zijn gerelateerd aan de introductie van de directe orale anticoagulantia. Deze medicamenten zijn inmiddels de eerste keuze behandeling voor de meerderheid van patiënten met acute longembolie. Onderzoek naar de effectiviteit en veiligheid van deze medicamenten bij patiënten met een maligniteit is op dit moment gaande. Daarnaast zal het gunstige bijwerkingenprofiel van de directe orale anticoagulantia gevolgen gaan hebben voor de keuze van de behandelduur. Door het lage risico op bloedingscomplicaties zullen artsen en patiënten waarschijnlijk sneller geneigd zijn de behandeling ook na een eerste veneuze trombo-embolie voor onbepaalde tijd te continueren. Dit zal belangrijke effecten hebben zoals hogere kosten maar het zal ook leiden tot een toenemende overbehandeling, lang niet alle patiënten met een veneuze trombo-embolie ontwikkelen immers een recidief. Daarnaast is het ook een hele interessante vraag of met het verlengen van de behandelduur alleen gedurende de behandeling een recidief wordt voorkomen of dat uiteindelijk het risico op een recidief afneemt en daarmee na verloop van de tijd de behandeling alsnog gestaakt zou kunnen worden. Wat betreft bij toeval gevonden longembolie in patiënten met kanker blijft de vraag of deze patiënten baat hebben bij antistollingstherapie. Indirect bewijs, zoals ook beschreven in dit proefschrift, suggereert dat het risico op een recidief veneuze trombo-embolie wordt verlaagd door antistollingstherapie en dat patiënten daarmee baat hebben bij behandeling met antistollingstherapie. Anderzijds is bekend dat patiënten met kanker ook een aanzienlijk hoger risico op bloedingscomplicaties hebben tijdens behandeling met antistollingstherapie. Het antwoord op deze vraag kan alleen definitief worden beantwoord door een gerandomiseerde studie waarin geen behandeling of eventueel een korte behandelduur wordt vergeleken met een behandeling voor onbepaalde duur, maar waarschijnlijk zal deze studie nooit verricht gaan worden en zullen we het moeten doen met indirect bewijs.

APPENDIX

List of publications

Dankwoord

Curriculum vitae

LIST OF PUBLICATIONS

den Exter PL, Hooijer J, **van der Hulle T**, van Oosten JP, Dekkers OM, Klok FA, Huisman MV. Vitamin K Antagonists Compared to Low-Molecular-Weight Heparins for Treatment of Cancer-Associated Venous Thromboembolism: An Observational Study in Routine Clinical Practice. An Observational Study in Routine Clinical Practice. Thromb Haemost. 2017 Oct 4;117(11). doi: 10.1160/TH-17-06-0382.

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CURRICULUM VITAE

Tom van der Hulle werd geboren op 3 mei 1984 te Zierikzee. In 2002 haalde hij zijn VWO diploma aan het Rijnlands Lyceum te Sassenheim. In datzelfde jaar startte hij met de studie Geneeskunde aan de Universiteit Leiden. De eerste ervaringen met onderzoek werden opgedaan tijdens de wetenschapsstage op de afdeling Ouderengeneeskunde en de afdeling Humane Genetica onder begeleiding van prof. dr. R.G.J. Westendorp en prof. dr. P. de Knijff. In 2006 vingen zijn coschappen aan en in 2008 behaalde hij zijn artsexamen. Aansluitend was hij werkzaam als arts-assistent niet in opleiding in het Medisch Centrum Haaglanden tot hij in 2009 kon beginnen met de opleiding tot internist in datzelfde ziekenhuis (opleiders dr. P.H.L.M. Geelhoed-Duijvestijn en dr. A.H. Bootsma). Sinds 2012 heeft hij zijn opleiding tot internist voortgezet in het Leids Universitair Medisch Centrum (opleider prof. dr. J.W. de Fijter). In 2013 begon hij aan wetenschappelijk onderzoek op de afdeling Trombose en Hemostase van het Leids Universitair Medisch Centrum onder begeleiding van prof. dr. M.V. Huisman, waarvan de resultaten zijn beschreven in dit proefschrift. Sinds 2016 is hij begonnen met het aandachtsgebied Medische Oncologie (opleiders prof. dr. A.J. Gelderblom en prof. dr. J.E.A. Portielje). Hij is getrouwd met Lotte Limburg met wie hij 2 kinderen heeft, Floor (2014) en Jacob (2016).